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Andrew Grey

Dated

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2. Patent application number (The Patent Office will fill in this part)	0000659.3		12 JAN 2000
3. Full name, address and postcode of the or of each applicant (underline all surnames)	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ		
Patents ADP number (if you know it)	6892673001		
If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom		
4. Title of the invention	METHOD		
5. Name of your agent (if you have one)	D YOUNG & CO		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	21 NEW FETTER LANE LONDON EC4A 1DA		
Patents ADP number (if you have one)	59006		
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Description 49 + 3 (SEQUENCE LISTING) + 173 (ANNEX) =
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Claims(s) 3

Abstract 1

Drawing(s) 0

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Priority documents

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Dr C T Harding

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METHOD

FIELD OF INVENTION

5 The present invention relates to a method. In particular, the present invention relates to an assay method.

10 More in particular, the present invention relates to an assay method for identifying whether a candidate agent can modulate the binding of gp120 to CCR5.

BACKGROUND ART

15 It is desirable to identify agents that can modulate the interaction of CCR5 and gp120. By way of background information, gp120 is the envelope protein of HIV that is required for viral entry into the target cells and CCR5 is the cellular receptor to the β -chemokines RANTES, Mip-1- α and Mip-1- β . CCR5 has been identified as being an important receptor in HIV infection.

20 WO-A-98/00535 discloses a method for detecting gp120 binding on the surface of cells bearing a co-receptor. The method uses directly labelled protein. This method requires high affinity interactions (low nanomolar Kd). However, the affinity of gp120 proteins from different HIV strains varies. Hence, it is believed that this method may not be capable or even suitable to identify agents that can modulate the interaction of
25 biologically relevant molecules.

WO-A-96/418884 discloses a method for screening for agents that may inhibit HIV-1 infection. That method utilises an antibody that, in itself, acts as an agent that would perturb CCR5 and gp120 binding. In addition the protein used in the specific
30 examples cannot bind CCR5. Hence, the specific target receptors are not CCR5.

WO-A-97/37005 discloses an assay method for detecting and preventing HIV infection. The assay described detects fusion of cells expressing gp160 with cells expressing CD4 and CCR5. It is believed that this assay has inherent problems as
35 containment and reagent provision issues would restrict the use of the method for high-throughput screening, particularly on a large scale.

US-A-5928881 discloses an assay that enables identification of CCR5 inhibitors. The assay requires directly labelled chemokine RANTES. We believe that this assay would not always be predictive of binding of gp120.

- 5 The present invention seeks to provide an effective assay method, readily adaptable to high throughput screening format, for identifying agents that would modulate medium to low affinity interactions of CCR5 with gp120.

SUMMARY ASPECTS OF THE PRESENT INVENTION

10

The present invention is based on the finding that *in vivo* the interaction of CCR5 with gp120 may be fairly weak. In this regard, our work with recombinant proteins suggests that the dissociation constant (K_d) of the interaction can be in the $10^{-7}M$ to $10^{-6}M$ range. This is contrast to the $10^{-9}M$ range described by others in model
15 systems and in, for example, the patent applications cited above (e.g. WO-A-98/00535 and references within).

The assay method of the present invention utilises this finding. It enables detection of such weak interaction.

20

For some applications, the assay method of the present invention may be described as being a competitive binding study between a candidate agent and the gp120/CCR5 combination.

25

DETAILED ASPECTS OF THE PRESENT INVENTION

In one aspect, the present invention relates to an assay method for determining whether an agent is capable of modulating the interaction of CCR5 with gp120; the method comprising: incubating the agent with CCR5 and gp120 to form a first
30 reaction mixture; and determining whether said agent modulates the interaction of CCR5 with gp120; wherein said gp120 is associated with CD4; and wherein said interaction is a low affinity binding.

35

In another aspect, the present invention relates to an agent identified by the method according to the present invention, wherein said agent is capable of modulating the interaction of CCR5 with gp120.

In a further aspect, the present invention relates to a process comprising the steps of:
(a) performing the assay according to the present invention; (b) identifying one or more agents that are capable of modulating the interaction of CCR5 with gp120; and (c) preparing a quantity of those one or more identified agents.

5

In a further aspect, the present invention relates to a method of affecting the *in vivo* interaction of CCR5 with gp120 with an agent; wherein the agent is capable of modulating the interaction of CCR5 with gp120 in an *in vitro* assay method; wherein the *in vitro* assay method is the assay method according to the present invention.

10

In a further aspect, the present invention relates to the use of an agent in the preparation of a pharmaceutical composition for the treatment of a disease or condition associated with the interaction of CCR5 with gp120, wherein the agent is the agent according to the present invention and/or wherein the agent is capable of modulating the interaction of CCR5 with gp120 when assayed *in vitro* by the assay method according to the present invention.

15

20

In a further aspect, the present invention relates to a method of treating a subject with an agent, wherein the agent is the agent of the present invention and/or wherein the agent is capable of modulating the interaction of CCR5 with gp120 when assayed *in vitro* by the assay method according to the present invention.

25

For ease of reference, these and further aspects of the present invention are now discussed under appropriate section headings. However, the teachings under each section are not necessarily limited to each particular section.

PREFERABLE ASPECTS

30

Preferably the method includes the step of adding a ligand to said first reaction mixture to form a second reaction mixture; wherein said ligand is capable of indicating whether said agent has modulated said interaction.

Preferably said ligand has a detectable label.

35

Preferably said detectable label is a atom or a group capable of emitting fluorescent light.

Preferably said fluorescent atom is Eu^{3+} .

Preferably detection consists of enhancing natural fluorescence of the Eu^{3+} atom by addition of an enhancer solution known to the art.

5

Preferably said ligand comprises at least a first antibody.

Preferably said first antibody is capable of binding to gp120; and wherein said binding is high affinity binding.

10

Preferably said first antibody is associated with a detectable label.

Preferably said ligand may comprise a second antibody.

15

Preferably said second antibody is capable of binding to said first antibody.

Preferably said second antibody is an anti-IgG antibody.

Preferably said detectable label is associated with said second antibody.

20

Preferably, the agent is capable of adversely modulating the weak binding interaction of CCR5 and gp120.

25

Examples of adverse modulation include the separation of, the prevention of the binding of, the cleavage of any one or more of, CCR5 and gp120 – and/or changing their folding configuration so that one or more of gp120 and CCR5 is inoperative.

30

Further examples of adverse modulation include the separation of, the prevention of the binding of, the cleavage of any one or more of, gp120 and CD4 – and/or changing their folding configuration so that one or more of gp120 and CD4 is inoperative.

ADVANTAGES

The present invention has a number of advantages. These advantages will be
5 apparent in the following description.

By way of example, the present invention is advantageous since it provides a
commercially useful assay to identify suitable agents that could be used *in vivo* to
treat conditions associated with CCR5/gp120 binding.

10 By way of further example, the present invention is advantageous since the method
detects interaction of gp120 with cells that express CCR5 alone.

By way of example, the present invention is advantageous since the method is
15 amenable to high throughput screening (HTS).

AMINO ACID SEQUENCE

As used herein, the term "amino acid sequence" is synonymous with the term
20 "polypeptide" and/or the term "protein". In some instances, the term "amino acid
sequence" is synonymous with the term "peptide". In some instances, the term
"amino acid sequence" is synonymous with the term "protein".

The amino acid sequence may be prepared isolated from a suitable source, or it may
25 be made synthetically or it may be prepared by use of recombinant DNA techniques.

In one aspect, the present invention provides an amino acid sequence that is capable
of acting as a target in an assay for the identification of one or more agents and/or
derivatives thereof capable of affecting gp120/CCR5 binding.

NUCLEOTIDE SEQUENCE

As used herein, the term "nucleotide sequence" is synonymous with the term
35 "polynucleotide".

The nucleotide sequence may be DNA or RNA of genomic or synthetic or of recombinant origin. The nucleotide sequence may be double-stranded or single-stranded whether representing the sense or antisense strand or combinations thereof.

5

For some applications, preferably, the nucleotide sequence is DNA.

For some applications, preferably, the nucleotide sequence is prepared by use of recombinant DNA techniques (e.g. recombinant DNA).

10

For some applications, preferably, the nucleotide sequence is cDNA.

For some applications, preferably, the nucleotide sequence may be the same as the naturally occurring form for this aspect.

15

In one aspect, the present invention provides a nucleotide sequence encoding a substance capable of acting as a target in an assay (such as a yeast two hybrid assay) for the identification of one or more agents and/or derivatives thereof capable of affecting the substance in order to modulate CCR5/gp120 binding.

20

VARIANTS/HOMOLOGUES/DERIVATIVES

In addition to the specific amino acid sequences and nucleotide sequences mentioned herein, the present invention also encompasses the use of variants, homologue and derivatives thereof. Here, the term "homology" can be equated with "identity".

25

In the present context, an homologous sequence is taken to include an amino acid sequence which may be at least 75, 85 or 90% identical, preferably at least 95 or 98% identical. In particular, homology should typically be considered with respect to those regions of the sequence (such as amino acids at positions 51, 56 and 57) known to be essential for an activity. Although homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions), in the context of the present invention it is preferred to express homology in terms of sequence identity.

30

35

Homology comparisons can be conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These commercially available computer programs can calculate % homology between two or more sequences.

5

% homology may be calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in one sequence is directly compared with the corresponding amino acid in the other sequence, one residue at a time. This is called an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of residues.

10

Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause the following amino acid residues to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence comparison methods are designed to produce optimal alignments that take into consideration possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting "gaps" in the sequence alignment to try to maximise local homology.

15

20

However, these more complex methods assign "gap penalties" to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared sequences - will achieve a higher score than one with many gaps. "Affine gap costs" are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimised alignments with fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is preferred to use the default values when using such software for sequence comparisons. For example when using the GCG Wisconsin Bestfit package (see below) the default gap penalty for amino acid sequences is -12 for a gap and -4 for each extension.

25

30

Calculation of maximum % homology therefore firstly requires the production of an optimal alignment, taking into consideration gap penalties. A suitable computer program for carrying out such an alignment is the GCG Wisconsin Bestfit package

35

(University of Wisconsin, U.S.A.; Devereux et al., 1984, *Nucleic Acids Research* 12:387). Examples of other software that can perform sequence comparisons include, but are not limited to, the BLAST package (see Ausubel et al., 1999 *ibid* – Chapter 18), FASTA (Atschul et al., 1990, *J. Mol. Biol.*, 403-410) and the GENEWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (see Ausubel et al., 1999 *ibid*, pages 7-58 to 7-60). However it is preferred to use the GCG Bestfit program.

Although the final % homology can be measured in terms of identity, the alignment process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled similarity score matrix is generally used that assigns scores to each pairwise comparison based on chemical similarity or evolutionary distance. An example of such a matrix commonly used is the BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin programs generally use either the public default values or a custom symbol comparison table if supplied (see user manual for further details). It is preferred to use the public default values for the GCG package, or in the case of other software, the default matrix, such as BLOSUM62.

Once the software has produced an optimal alignment, it is possible to calculate % homology, preferably % sequence identity. The software typically does this as part of the sequence comparison and generates a numerical result.

The sequences may also have deletions, insertions or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent substance. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues as long as the secondary binding activity of the substance is retained. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine, valine, glycine, alanine, asparagine, glutamine, serine, threonine, phenylalanine, and tyrosine.

Conservative substitutions may be made, for example according to the Table below. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar – uncharged	C S T M
		N Q
	Polar – charged	D E
		K R
AROMATIC		H F W Y

EXPRESSION VECTORS

- 5 The nucleotide sequence for use as the target or for expressing the target can be incorporated into a recombinant replicable vector. The vector may be used to replicate and express the nucleotide sequence in and/or from a compatible host cell. Expression may be controlled using control sequences which include promoters/enhancers and other expression regulation signals. Prokaryotic promoters and promoters functional in eukaryotic cells may be used. Tissue specific or stimuli specific promoters may be used. Chimeric promoters may also be used comprising sequence elements from two or more different promoters described above.

- 15 The protein produced by a host recombinant cell by expression of the nucleotide sequence may be secreted or may be contained intracellularly depending on the sequence and/or the vector used. The coding sequences can be designed with signal sequences which direct secretion of the substance coding sequences through a particular prokaryotic or eukaryotic cell membrane.

20 FUSION PROTEINS

- The target amino acid sequence may be produced as a fusion protein, for example to aid in extraction and purification. Examples of fusion protein partners include glutathione-S-transferase (GST), 6xHis, GAL4 (DNA binding and/or transcriptional activation domains) and (-galactosidase. It may also be convenient to include a proteolytic cleavage site between the fusion protein partner and the protein sequence of interest to allow removal of fusion protein sequences. Preferably the fusion protein will not hinder the activity of the target.

The fusion protein may comprise an antigen or an antigenic determinant fused to the substance of the present invention. In this embodiment, the fusion protein may be a non-naturally occurring fusion protein comprising a substance which may act as an adjuvant in the sense of providing a generalised stimulation of the immune system. The antigen or antigenic determinant may be attached to either the amino or carboxy terminus of the substance.

In another embodiment of the invention, the amino acid sequence may be ligated to a heterologous sequence to encode a fusion protein. For example, for screening of peptide libraries for agents capable of affecting the substance activity, it may be useful to encode a chimeric substance expressing a heterologous epitope that is recognized by a commercially available antibody.

CCR5

An essential component of the assay is CCR5.

CCR5 is a chemokine receptor that typically is present on the surfaces of certain cells within the human body.

The term "chemokine", is a contraction of "chemotactic cytokines". The chemokines comprise a large family of proteins which have in common important structural features and which have the ability to attract leukocytes. As leukocyte chemotactic factors, chemokines play an indispensable role in the attraction of leukocytes to various tissues of the body, a process which is essential for both inflammation and the body's response to infection. Because chemokines and their receptors are central to the pathophysiology of inflammatory and infectious diseases, agents which are active in modulating, preferably antagonizing, the activity of chemokines and their receptors, are useful in the therapeutic treatment of such inflammatory and infectious diseases.

The chemokine receptor CCR5 is of particular importance in the context of treating inflammatory and infectious diseases. CCR5 is a receptor for chemokines, especially for the macrophage inflammatory proteins (MIP) designated MIP-1 α and MIP-1 β , and for a protein which is regulated upon activation and is normal T-cell expressed and secreted (RANTES).

Background teachings on CCR5 may be found in WO-A-97/32019.

The nucleotide sequence encoding same and the amino acid sequence for same are presented in the attached sequence listings.

Background teachings on CCR5 have also been presented by Victor A. McKusick *et al* on <http://www.ncbi.nlm.nih.gov/Omim>. The following information concerning CCR5 has been extracted from that source.

"Samson et al. (1996) cloned a human C-C chemokine receptor gene from a human genomic DNA library based on its similarity to a murine C-C chemokine receptor clone (MOP020). The human gene, which they designated ChemR13, encodes a 352-amino acid protein (designated CCKR5 by them) with a calculated molecular mass of 40,600 Da and a potential N-linked glycosylation site. With a set of overlapping lambda clones, they showed that the gene is 17.5 kb from the CMKBR2 gene. The 2 coding regions share 75% DNA and amino acid sequence identity.

Samson et al. (1996) functionally expressed the gene in a stably transfected CHO-K1 cell line. In transfected cells, macrophage inflammatory protein (MIP)-1- α appeared to be the most potent agonist for CCKR5, with MIP-1- β and RANTES also active at physiologic concentrations. Samson et al. (1996) detected transcript from the gene in a promyeloblastic cell line, which suggested a potential role for the chemokine receptor in granulocyte lineage proliferation and differentiation.

By radiation hybrid mapping, Liu et al. (1996) localized the CCR5 gene (designated CKR5 by them) to chromosome 3p21.

The C-C chemokine receptor CMKBR5 was identified as a coreceptor for the human immunodeficiency virus-1 (HIV-1) by Deng et al. (1996) and Dragic et al. (1996). CMKBR5 and fusin (162643) facilitate the fusion of HIV-1 with the plasma membrane of CD4(+) cells (CD4; 186940). Deng et al. (1996) found that CMKBR5, and not fusin, promotes entry of the macrophage-tropic viruses believed to be the key pathogenic strains *in vivo*. Dragic et al. (1996) showed that MIP-1- α , MIP-1- β , and RANTES each inhibit infection of CD4(+) cells by primary, nonsyncytium-inducing (NSI) HIV-1 strains at the virus entry stage and also block env-mediated cell-cell fusion. Both groups showed that expression of the CCKR5 protein renders nonpermissive CD4(+) cells susceptible to infection by HIV-1 strains. Alkhatib et al. (1996) reported similar observations and detected mRNA for the receptor only in cell types susceptible to macrophage-tropic isolates of HIV-1. See also Choe et al. (1996), who implicated both CCR5 and CCR3 in the ability of HIV-1 to infect cells expressing those receptors.

Some individuals remain uninfected by HIV-1 despite repeated exposure to the virus. Both

Liu et al. (1996) and Samson et al. (1996) identified a molecular basis for such HIV-1 resistance. Samson et al. (1996) postulated that variants of the CMKBR5 gene may be responsible for relative or absolute resistance to HIV-1 infection. In an HIV-1-infected patient with slow disease progression, Samson et al. (1996) identified a heterozygous 32-bp deletion in the CMKBR5 gene that results in a frameshift and premature termination of translation of the transcript. Liu et al. (1996) identified the same homozygous 32-bp deletion with CMKBR5 in 2 individuals who, though multiply exposed to HIV-1 infection, remained uninfected. Liu et al. (1996) found that the deletion comprises nucleotides 794 to 825 of the cDNA sequence and results in a reading frameshift after amino acid 174, inclusion of 7 novel amino acids, and truncation at codon 182. They showed that the severely truncated protein could not be detected at the surface of cells that normally express the protein. Samson et al. (1996) stated that the mutant protein lacks the last 3 of 7 putative transmembrane regions of the receptor as well as regions involved in G protein coupling and signal transduction. Through in vitro fusion assays, both Liu et al. (1996) and Samson et al. (1996) determined that the truncated receptor did not allow fusion of CD4(+) cells with cells expressing env protein from either macrophage-tropic or dual-tropic viruses. Samson et al. (1996) found that coexpression of the deletion mutant with wildtype CCR5 reduced the fusion efficiency of 2 different viral envelope proteins in 3 independent experiments.

Dean et al. (1996) reported results of their CKR5 studies in 1,955 individuals included in 6 well-characterized AIDS cohort studies. They identified 17 individuals who were homozygous for the CKR5 32-bp deletion allele (601373.0001). Deletion homozygotes occurred exclusively among the 612 members of the HIV-1-exposed, antibody-negative group and not at all in 1,343 HIV-1 infected individuals. The frequency of the CKR5 deletion heterozygotes was significantly elevated in groups of individuals who had survived HIV-1 infection for more than 10 years. In some risk groups the frequency of CKR5 deletion heterozygotes was twice as frequent as in groups with rapid progressors to AIDS. Survival analysis clearly showed that the disease progression was slower in CKR5 deletion heterozygotes than in individuals homozygous for the normal CKR5 allele. Dean et al. (1996) postulated that the CKR5 32-bp deletion may act as 'a recessive restriction gene against HIV-1 infection' and may exert a dominant phenotype of delayed progression to AIDS among infected individuals. Dean et al. (1996) reported that in addition to the CKR5 32-bp deletion allele, they found unique single-strand conformation polymorphisms (SSCPs) in other patients, some of whom were long-term nonprogressors. They speculated that at least some of these alleles disrupt CKR5 function and inhibit the spread of HIV-1 or the progression to AIDS. Dean et al. (1996) recommended that the entire coding region of CKR5 be screened in nonprogressors and in rapid progressors to identify other CKR5 variants.

To determine the role of the 32-bp deletion in CKR5 in HIV-1 transmission and disease progression, Huang et al. (1996) analyzed the CKR5 genotype of 1,252 homosexual men enrolled in the Chicago component of the Multicenter AIDS Cohort Study. No infected participant was found to be homozygous for the 32-bp deletion allele, whereas 3.6% of at-risk

but uninfected Caucasian participants were homozygous, showing the highly protective role of this genotype against sexual acquisition of HIV-1. No evidence was found that suggested heterozygotes were protected against HIV-1 infection, but a limited protective role against disease progression was noted.

5 Zimmerman et al. (1997) reported results of a large study that analyzed the frequency of the 32-bp deletion allele of CMKBR5 in populations from North America, Asia, and Africa. Ansari-Lari et al. (1997) also published data on the population frequencies of various mutations in CCR5. The study indicated that the mutations are relatively specific to different ethnicities; apart from the 32-bp deletion allele in the American Caucasian population, and 2
10 alleles in Chinese and Japanese populations, the CCR5 locus did not show a high degree of genetic variation. The authors stated that, while additional population screening at this locus might identify other sequence variants, their frequencies are likely to be less than 0.01. The frequency of the 32-bp deletion allele in American Caucasians was approximately 0.16, a value somewhat higher than that previously reported for this group.

15 Smith et al. (1997) analyzed 2-locus genotypes and found that the 32-bp deletion at the CCR5 locus and the 64I allele at the CCR2 locus are in strong, perhaps complete, linkage disequilibrium with each other. This means that CCR5-del32 invariably occurs on a chromosome with allele CCR2-64V, whereas CCR2-64I occurs on a chromosome that has the wildtype (undeleted) allele at the CCR5 locus. Thus, they could estimate the independent
20 effects of the CCR2 and CCR5 polymorphisms. An estimated 38 to 45% of AIDS patients who had rapid progression of less than 3 years from HIV-1 exposure to onset of AIDS symptoms could be attributed to their wildtype status at one or the other of these loci, whereas the survival of 28 to 29% of long-term survivors, who avoided AIDS for 16 years or more, could be explained by a mutant genotype for CCR2 or CCR5.

25 Biti et al. (1997) reported an HIV-infected, asymptomatic individual of European descent who was found to be homozygous for the 32-bp deletion. The presence of homozygosity was supported by genotyping his sole surviving parent (a heterozygote) and his sibs (a CCR5-del32 homozygous brother, a heterozygous brother, and a CCR5 wildtype homozygous sister). The patient presented in 1992 with a seroconversion-like illness of 1-month duration, at which
30 time he was diagnosed HIV-1 seropositive by Western blot. At the time of their report, his CD4+ T-cell count was 460, and a plasma RNA viral load test showed 19,000 copies per milliliter. Biti et al. (1997) noted that the tropism of the infecting HIV-1 strain was still under investigation.

Using a panel of monoclonal antibodies specific for human CCR5, Rottman et al. (1997)
35 showed by immunohistochemistry and flow cytometry that CCR5 is expressed by bone marrow-derived cells known to be targets for HIV-1 infection, including a subpopulation of lymphocytes and monocytes/macrophages in blood, primary and secondary lymphoid organs, and noninflamed tissues. In the central nervous system, CCR5 was expressed on neurons, astrocytes, and microglia. In other tissues, CCR5 was expressed on epithelium, endothelium,
40 vascular smooth muscle, and fibroblasts. Chronically inflamed tissues contained an increased

number of CCR5-positive mononuclear cells, and the number of immunoreactive cells was directly associated with a histopathologic correlate of inflammatory severity. The results suggested that CCR5-positive cells are recruited to inflammatory sites and, as such, may facilitate transmission of macrophagetropic strains of HIV-1.

5 Cohen et al. (1997) studied a cohort of 33 HIV-1 nonprogressors and compared 21 patients who were homozygous wildtype at the CCR5 locus with 12 who were heterozygous for the 32-bp deletion mutation in CCR5. There were no differences in CD4+ or CD8+ T-cell counts, or in plasma or lymph node viral loads. The authors concluded that CCR5 is not the sole determinant of long-term nonprogression in some HIV-1 infected individuals. Although no
10 differences were detected at an average of 11 years postinfection, the authors suggest that CCR5 may still play a role in nonprogression by limiting viral replication during acute infection.

Although CD4 was identified initially as the cellular receptor for HIV, several lines of evidence indicated that expression of CD4 alone was insufficient to confer susceptibility to
15 infection by the virus. Specifically, HIV did not infect mouse cells transfected with a human CD4 expression vector or mice transgenic for the expression of human CD4. Furthermore, although HIV binding and internalization can be mediated by CD4 acting together with one of several members of the chemokine receptor superfamily, CCR5 appears to be the critical coreceptor used by HIV in the initial stages of infection. However, because mouse CCR5
20 differs significantly from human CCR5, it cannot function as a coreceptor for HIV, and thus, expression of human CD4 alone is insufficient to permit entry of HIV into mouse cells. Browning et al. (1997) found that mice transgenic for both CD4 and CCR5 are susceptible to HIV infection.

Zagury et al. (1998) found that there were factors other than the CCR5 polymorphism
25 accounting for the fact that exposure to HIV-1 does not usually lead to infection. Although this fact could be because of insufficient virus titer, there is abundant evidence that some individuals resist infection even when directly exposed to a high titer of HIV. This protection is related to homozygous mutations in CCR5, the receptor for the β -chemokines, and earlier studies had shown that the same chemokines markedly suppressed the nonsyncytial inducing
30 variants of HIV-1, the chief virus type transmitted from person to person. However, CCR5 mutations are not likely to be the unique mechanism of protection because HIV-1 variants can use other chemokine receptors as their coreceptor and, indeed, infection has been demonstrated within the presence of such mutations. Zagury et al. (1998) found transient natural resistance over time of most of 128 hemophiliacs who were inoculated repeatedly with
35 HIV-1-contaminated factor VIII concentrate from plasma during 1980 to 1985, before the development of the HIV blood test. Furthermore, and remarkably, 14 subjects remained unaffected to the time of the report, and in these subjects homozygous CCR5 mutations were found in none, but in most of them there was overproduction of β -chemokines. In vitro experiments confirmed the potent anti-HIV suppressive effect of these chemokines. The
40 chemokines studied were generically referred to as MMR, an abbreviation for MIP-1- α , MIP-

1- β , and RANTES.

Martin et al. (1998) showed by genetic association analysis of 5 cohorts of people with AIDS that infected individuals homozygous for a multisite haplotype of the CCR5 regulatory region containing the promoter allele, CCR5P1, progress to AIDS more rapidly than those with other CCR5 promoter genotypes, particularly in the early years after infection. Composite genetic epidemiologic analyses of the genotypes bearing CCR5P1, CCR5-delta-32, CCR2-64I (see 601267), and SDF1-3-prime A (see 600835) affirmed distinct regulatory influences for each gene on AIDS progression. An estimated 10 to 17% of patients who developed AIDS within 3.5 years of HIV-1 infection did so because they were homozygous for CCR5P1/P1, and 7 to 13% of all people carry this susceptible genotype. The cumulative and interactive influence of these AIDS restriction genes illustrates the multigenic nature of host factors limiting AIDS disease progression.

CCR5 and CCR2 are tightly linked on 3p22-p21, separated by 20 kb. Common allelic variants in both genes are associated with slower progression to AIDS after infection. The protective influences of CCR5-delta-32 and CCR2-64I are independent in AIDS cohorts, and the 2 mutations have never been found on the same chromosome haplotype. The physical proximity of CCR2 and CCR5, the equivalent functional efficiency of alternative CCR2 allelic products as chemokine or HIV-1 coreceptors, and the rarity of HIV-1 strains that use the CCR2 receptor led to the speculation that CCR2-64I may be hitchhiking (or tracking by linkage disequilibrium) with an undiscovered CCR5 variant, perhaps in the cis-regulatory region, that is directly responsible for the CCR2-64I protective effect. Martin et al. (1998) found that among 2,603 individuals enrolled in 5 AIDS cohorts, CCR2-64I was always found on a CCR5P1-bearing haplotype and that CCR5-delta-32 was consistently found on a CCR5P1 haplotype as well. All CCR2-64I/64I homozygotes were always CCR5P1/P1 homozygotes (N = 43). Similarly, all CCR5-delta-32/delta-32 homozygotes were CCR5P1/P1 homozygotes (N = 18). Finally, none of 657 individuals who lacked the CCR5P1 allele had either the CCR5-delta-32 or the CCR2-64I allele. Thus the entire CCR2-CCR5 complex can be considered as a 6-allele genotype system, based on the composite CCR2 and CCR5 haplotype.

In a denaturing high-pressure liquid chromatography (DHPLC) screen of AIDS patients, Martin et al. (1998) detected 4 common allelic variants (CCR5P1-P4); 6 rare alleles (CCR5P5-P10) were discovered as heterozygotes upon subsequent single-strand conformation polymorphism (SSCP) screening of 5 AIDS cohorts. Sequence analysis of the CCR5 promoter region of individuals homozygous for the CCR5P1-P4 variants and heterozygotes of the 6 rare variants revealed 10 polymorphic nucleotide positions that described 10 CCR5 promoter haplotype alleles, referred to as promoter alleles. McDermott et al. (1998) reported a G/T variant, corresponding to position 303 of the promoter region, that showed an epidemiologic association with rapid progression to AIDS.

Farzan et al. (1999) showed that the chemokine receptor CCR5, a principal HIV-1 coreceptor, is posttranslationally modified by O-linked glycosylation and by sulfation of its N-terminal tyrosines. Sulfated tyrosines contributed to the binding of CCR5 to MIP-1- α , MIP-1- β , and

HIV-1 gp120/CD4 complexes, and to the ability of HIV-1 to enter cells expressing CCR5 and CD4. Farzan et al. (1999) concluded that tyrosine sulfation may contribute to the natural function of many 7-transmembrane-segment receptors and may be a modification common to primate immunodeficiency virus coreceptors.

5 Carrington et al. (1999) reviewed the growing number of genetic variants within the coding and 5-prime regulatory region of CCR5 that had been identified, several of which have functional consequences for HIV-1 pathogenesis. The findings provided logic for the development of therapeutic strategies that target the interaction of HIV-1 envelope and CCR5 in HIV-1 associated disease."

10 gp120

An essential component of the assay is gp120. Information on gp120 has been presented above. Further teachings on gp120 may be found in the art, such as in
15 some of the patent applications cited above.

The nucleotide sequence encoding gp120 and the amino acid sequence for same are presented in the attached sequence listings.

20 CD4

In the assay of the present invention the gp120 is typically associated with CD4. A suitable CD4 is a commercially available soluble version of CD4 (baculovirus expressed sCD4). In the preparation of the first reaction mixture, the gp120 and the
25 CD4 may be added sequentially, simultaneously or together.

Background teachings on CD4 are mentioned above.

Background teachings on CD4 may also be found in WO-A-89/03222. The
30 nucleotide sequence encoding same and the amino acid sequence of same is presented in the attached sequence listings.

In addition, further background teachings on CD4 have been presented by Victor A. McKusick *et al* on <http://www.ncbi.nlm.nih.gov/Omim>. The following further
35 information concerning CD4 has been extracted from that source.

"Circulating mature T lymphocytes constitute a heterogeneous cell population with 2 major phenotypes, one expressing the CD4 marker on its surface (generally associated with helper/inducer function), and the other expressing the CD8 antigen (usually associated with cytotoxic/suppressor activity). Amadori et al. (1995) noted that evaluation of the CD4/CD8 ratio is routine in AIDS patients for the assessment of immune function and added that not only HIV infection but also other acute viral diseases, such as infections by cytomegalovirus, Epstein-Barr virus, and influenza virus, are usually associated with an inversion of the CD4/CD8 ratio. A low ratio is also a hallmark of intense, chronic immune responses, such as allograft rejection and graft-versus-host disease. CD4/CD8 ratios of 1.5 to 2.5 are usually considered normal. The occasional finding of a CD4/CD8 ratio less than 1 in otherwise normal, healthy individuals is usually disregarded.

Because of a personal interest on the part of one member of the group (A.A.) who had shown an invariable ratio less than 1 over many years, and because the ratio in mice was shown by Kraal et al. (1983) to be under genetic control, Amadori et al. (1995) studied the genetic pattern of inheritance of the ratio in a population of 468 healthy blood donors. Distribution of the ratio in males and females was significantly different and was significantly affected by age. In 46 randomly selected families, the parental CD4/CD8 ratios significantly influenced the ratio in offspring. Complex segregation analysis of the data rejected the non-genetic hypothesis; among the genetic models tested, a major recessive gene with a polygenic component and random environmental effects was the most parsimonious model. Overall, Amadori et al. (1995) found that 57% of the variation in the CD4/CD8 ratio could be attributed to genetic factors, as opposed to noninherited (stochastic or environmental) factors. In mice, the CD4/CD8 ratio appears to be under the genetic control of a single dominant gene (Kraal et al., 1983). Chakravarti (1995) pointed to several important implications of the simple observation in this study. First, norms for the ratio must be defined separately for different ages, genders, and perhaps even populations. The possibility of a major gene determining the ratio implies that family history of low ratios may need to be considered for accurate prognosis of HIV or other infection. The identification of genes underlying this phenotype will lead to a better understanding of the mechanisms that commit immature thymocytes to the helper or cytotoxic lineages, and the site in the developmental chain in which they function. Lastly, identification of the genes will also help answer questions regarding genetic factors that control infection and immunity.

To define the mode of inheritance of the CD4/CD8 ratio, Clementi et al. (1999) examined the absolute number of CD4 and CD8 cells in a large unselected control population and in members of 70 nuclear families. Pedigrees of nuclear families were analyzed by complex segregation analysis. Data were adjusted before this analysis to remove the effects of relevant covariates. The nongenetic transmission and the multifactorial model could be easily rejected for both CD4 and CD8 cells. The best fitting models were a major autosomal recessive gene with a residual multifactorial effect controlling the high number of CD4 and a major autosomal recessive gene with a residual multifactorial effect controlling the high number of

CD8 cells. The authors pointed out that the knowledge of the CD4+ cell number and the proportion between CD4+ and CD8+ T cells could be a useful parameter in predicting human immunodeficiency virus infection outcome."

5 LOW AFFINITY BINDING

As used in relation to the present invention, preferably the term "low affinity binding" means a Kd value of at least about 200 nM. More preferably the term "low affinity binding" means a Kd value of more than about 200 nM.

10

LIGAND

In a preferred aspect, the assay method of the present invention utilises a ligand. This ligand is capable of indicating whether said agent has modulated said
15 interaction.

The ligand may be any suitable ligand. The ligand may be an organic chemical compound. The ligand may be a protein.

20 In a preferred aspect, the ligand carries a detectable label. This detectable label may become detectable once modulation has occurred – such as through a change in spectrometric properties of the ligand.

This label may be detectable by, for example, spectrometric means – such as
25 spectrophotometric means. Preferably, however, the detectable label is a fluorescent label. Here, any suitable fluorescent can be used.

In a preferred aspect, the ligand comprises at least one antibody, preferably at least two antibodies. In this respect, the at least one antibody is termed a "first antibody".
30 This first antibody may be able to bind to any of the agent to gp120. In a preferred aspect, the first antibody is able to bind to gp120 with high affinity and specificity, and in a mode that does not disturb the interaction of gp120 with either CD4 or CCR5.

If the ligand comprises at least two antibodies, then the at least one other antibody is
35 called a "second antibody". The second antibody may be able to bind the first antibody. In a preferred aspect, the second antibody is able to bind to the first

antibody with high affinity and specificity, and in a way that does not disturb the interaction of the first antibody with its ligand.

Preferably, the ligand comprises the first antibody and the second antibody. In this embodiment, in the preparation of the second reaction mixture the first antibody and the second antibody may be added sequentially, simultaneously or together.

Preferably the second antibody carries the detectable label. If there is no second antibody, the first antibody typically carries the detectable label.

ANTIBODY

As indicated, preferably the ligand for use in the assay method of the present invention comprises one or two antibodies.

The "antibody" as used herein includes but is not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments and fragments produced by a Fab expression library. Such fragments include fragments of whole antibodies which retain their binding activity for a target substance, Fv, F(ab') and F(ab')₂ fragments, as well as single chain antibodies (scFv), fusion proteins and other synthetic proteins which comprise the antigen-binding site of the antibody. Furthermore, the antibodies and fragments thereof may be humanised antibodies, for example as described in US-A-239400. Neutralizing antibodies, i.e., those which inhibit biological activity of the substance polypeptides, are especially preferred for diagnostics and therapeutics.

Antibodies may be produced by standard techniques, such as by immunisation with the substance of the invention or by using a phage display library.

If polyclonal antibodies are desired, a selected mammal (e.g., mouse, rabbit, goat, horse, etc.) is immunised with an immunogenic polypeptide bearing an epitope(s) obtainable from an identified agent and/or substance of the present invention. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminium hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol. BCG (Bacilli Calmette-Guerin) and Corynebacterium parvum are potentially useful human adjuvants which may be employed if purified the

substance polypeptide is administered to immunologically compromised individuals for the purpose of stimulating systemic defence.

5 Serum from the immunised animal is collected and treated according to known procedures. If serum containing polyclonal antibodies to an epitope obtainable from an identified agent and/or substance of the present invention contains antibodies to other antigens, the polyclonal antibodies can be purified by immunoaffinity chromatography. Techniques for producing and processing polyclonal antisera are known in the art. In order that such antibodies may be made, the invention also
10 provides polypeptides of the invention or fragments thereof haptenised to another polypeptide for use as immunogens in animals or humans.

Monoclonal antibodies directed against particular epitopes can also be readily produced by one skilled in the art. The general methodology for making monoclonal
15 antibodies by hybridomas is well known. Immortal antibody-producing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. Panels of monoclonal antibodies produced against orbit epitopes can be screened for various properties; i.e., for isotype and epitope affinity.

20

Monoclonal antibodies may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique originally described by Koehler and Milstein (1975 Nature 256:495-497), the human B-cell hybridoma technique (Kosbor
25 et al (1983) Immunol Today 4:72; Cote et al (1983) Proc Natl Acad Sci 80:2026-2030) and the EBV-hybridoma technique (Cole et al (1985) Monoclonal Antibodies and Cancer Therapy, Alan R Liss Inc, pp 77-96). In addition, techniques developed for the production of "chimeric antibodies", the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and
30 biological activity can be used (Morrison et al (1984) Proc Natl Acad Sci 81:6851-6855; Neuberger et al (1984) Nature 312:604-608; Takeda et al (1985) Nature 314:452-454). Alternatively, techniques described for the production of single chain antibodies (US Patent No. 4,946,779) can be adapted to produce the substance specific single chain antibodies.

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening recombinant immunoglobulin libraries or panels of highly specific binding reagents as disclosed in Orlandi et al (1989, Proc Natl Acad Sci 86: 3833-3837), and Winter G and Milstein C (1991; Nature 349:293-299).

Antibody fragments which contain specific binding sites for the substance may also be generated. For example, such fragments include, but are not limited to, the F(ab')₂ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity (Huse WD et al (1989) Science 256:1275-1281).

ASSAY

Any one or more of appropriate targets - such as an amino acid sequence and/or nucleotide sequence - may be used for identifying an agent capable of modulating the interaction of gp120 with CCR5 in any of a variety of drug screening techniques. The target employed in such a test may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The abolition of target activity or the formation of binding complexes between the target and the agent being tested may be measured.

The assay of the present invention may be a screen, whereby a number of agents are tested. In one aspect, the assay method of the present invention is a high through put screen.

Techniques for drug screening may be based on the method described in Geysen, European Patent Application 84/03564, published on September 13, 1984. In summary, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with a suitable target or fragment thereof and washed. Bound entities are then detected - such as by appropriately adapting methods well known in the art. A purified target can also be coated directly onto plates for use in a drug screening techniques. Alternatively, non-neutralising antibodies can be used to capture the peptide and immobilise it on a solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralising antibodies capable of binding a target specifically compete with a test compound for binding to a target.

5

Another technique for screening provides for high throughput screening (HTS) of agents having suitable binding affinity to the substances and is based upon the method described in detail in WO-A-84/03564.

10

It is expected that the assay methods of the present invention will be suitable for both small and large-scale screening of test compounds as well as in quantitative assays.

15

In one preferred aspect, the present invention relates to a method of identifying agents that selectively modulate the interaction between gp120 and CCR5.

20

In a preferred aspect, the assay of the present invention utilises cells that display CCR5 on their surface. These cells may be isolated from a subject possessing such cells. However, preferably, the cells are prepared by transfecting cells so that upon transfect those cells display on their surface CCR5. Teachings for preparing such transfected cells may be found in US-A-5939320.

REPORTERS

25

A wide variety of reporters may be used in the assay methods (as well as screens) of the present invention with preferred reporters providing conveniently detectable signals (eg. by spectroscopy). By way of example, a reporter gene may encode an enzyme which catalyses a reaction which alters light absorption properties.

30

Other protocols include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and fluorescent activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilising monoclonal antibodies reactive to two non-interfering epitopes may even be used. These and other assays are described, among other places, in Hampton R et al (1990, Serological Methods, A Laboratory Manual, APS Press, St Paul MN) and Maddox DE et al (1983, J Exp Med 15 8:121 1).

35

Examples of reporter molecules include but are not limited to (galactosidase, invertase, green fluorescent protein, luciferase, chloramphenicol, acetyltransferase, (glucuronidase, exo-glucanase and glucoamylase. Alternatively, radiolabelled or fluorescent tag-labelled nucleotides can be incorporated into nascent transcripts which are then identified when bound to oligonucleotide probes.

By way of further examples, a number of companies such as Pharmacia Biotech (Piscataway, NJ), Promega (Madison, WI), and US Biochemical Corp (Cleveland, OH) supply commercial kits and protocols for assay procedures. Suitable reporter molecules or labels include those radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles and the like. Patents teaching the use of such labels include US-A-3817837; US-A-3850752; US-A-3939350; US-A-3996345; US-A-4277437; US-A-4275149 and US-A-4366241.

HOST CELLS

Polynucleotides for use in the present invention – such as for use as targets or for expressing targets - may be introduced into host cells.

The term "host cell" - in relation to the present invention includes any cell that could comprise the target for the agent of the present invention.

Here, polynucleotides may be introduced into prokaryotic cells or eukaryotic cells, for example yeast, insect or mammalian cells.

Polynucleotides of the invention may introduced into suitable host cells using a variety of techniques known in the art, such as transfection, transformation and electroporation. Where polynucleotides of the invention are to be administered to animals, several techniques are known in the art, for example infection with recombinant viral vectors such as retroviruses, herpes simplex viruses and adenoviruses, direct injection of nucleic acids and biolistic transformation.

Thus, a further embodiment of the present invention provides host cells transformed or transfected with a polynucleotide that is or expresses the target of the present invention. Preferably said polynucleotide is carried in a vector for the replication and

expression of polynucleotides that are to be the target or are to express the target. The cells will be chosen to be compatible with the said vector and may for example be prokaryotic (for example bacterial), fungal, yeast or plant cells.

5 The gram negative bacterium *E. coli* is widely used as a host for heterologous gene expression. However, large amounts of heterologous protein tend to accumulate inside the cell. Subsequent purification of the desired protein from the bulk of *E. coli* intracellular proteins can sometimes be difficult.

10 In contrast to *E. coli*, bacteria from the genus *Bacillus* are very suitable as heterologous hosts because of their capability to secrete proteins into the culture medium. Other bacteria suitable as hosts are those from the genera *Streptomyces* and *Pseudomonas*.

15 Depending on the nature of the polynucleotide encoding the polypeptide of the present invention, and/or the desirability for further processing of the expressed protein, eukaryotic hosts such as yeasts or other fungi may be preferred. In general, yeast cells are preferred over fungal cells because they are easier to manipulate. However, some proteins are either poorly secreted from the yeast cell, or in some
20 cases are not processed properly (e.g. hyperglycosylation in yeast). In these instances, a different fungal host organism should be selected.

Examples of suitable expression hosts within the scope of the present invention are fungi such as *Aspergillus* species (such as those described in EP-A-0184438 and
25 EP-A-0284603) and *Trichoderma* species; bacteria such as *Bacillus* species (such as those described in EP-A-0134048 and EP-A-0253455), *Streptomyces* species and *Pseudomonas* species; and yeasts such as *Kluyveromyces* species (such as those described in EP-A-0096430 and EP-A-0301670) and *Saccharomyces* species. By way of example, typical expression hosts may be selected from *Aspergillus niger*,
30 *Aspergillus niger* var. *tubigenis*, *Aspergillus niger* var. *awamori*, *Aspergillus aculeatis*, *Aspergillus nidulans*, *Aspergillus oryzae*, *Trichoderma reesei*, *Bacillus subtilis*, *Bacillus licheniformis*, *Bacillus amyloliquefaciens*, *Kluyveromyces lactis* and *Saccharomyces cerevisiae*.

Polypeptides that are extensively modified may require correct processing to complete their function. In those instances, mammalian cell expression systems (such as HEK-293, CHO, HeLA) are required, and the polypeptides are expressed either intracellularly, on the cell membranes, or secreted in the culture media if preceded by an appropriate leader sequence.

The use of suitable host cells - such as yeast, fungal, plant and mammalian host cells - may provide for post-translational modifications (e.g. myristoylation, glycosylation, truncation, lipidation and tyrosine, serine or threonine phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the present invention.

ORGANISM

The term "organism" in relation to the present invention includes any organism that could comprise the target according to the present invention and/or products obtained therefrom. Examples of organisms may include a fungus, yeast or a plant.

The term "transgenic organism" in relation to the present invention includes any organism that comprises the target according to the present invention and/or products obtained.

TRANSFORMATION OF HOST CELLS/HOST ORGANISMS

As indicated earlier, the host organism can be a prokaryotic or a eukaryotic organism. Examples of suitable prokaryotic hosts include *E. coli* and *Bacillus subtilis*. Teachings on the transformation of prokaryotic hosts is well documented in the art, for example see Sambrook *et al* (Molecular Cloning: A Laboratory Manual, 2nd edition, 1989, Cold Spring Harbor Laboratory Press) and Ausubel *et al.*, Current Protocols in Molecular Biology (1995), John Wiley & Sons, Inc.

If a prokaryotic host is used then the nucleotide sequence may need to be suitably modified before transformation - such as by removal of introns.

In another embodiment the transgenic organism can be a yeast. In this regard, yeast have also been widely used as a vehicle for heterologous gene expression. The

species *Saccharomyces cerevisiae* has a long history of industrial use, including its use for heterologous gene expression. Expression of heterologous genes in *Saccharomyces cerevisiae* has been reviewed by Goodey et al (1987, Yeast Biotechnology, D R Berry et al, eds, pp 401-429, Allen and Unwin, London) and by King et al (1989, Molecular and Cell Biology of Yeasts, E F Walton and G T Yarronton, eds, pp 107-133, Blackie, Glasgow).

For several reasons *Saccharomyces cerevisiae* is well suited for heterologous gene expression. First, it is non-pathogenic to humans and it is incapable of producing certain endotoxins. Second, it has a long history of safe use following centuries of commercial exploitation for various purposes. This has led to wide public acceptability. Third, the extensive commercial use and research devoted to the organism has resulted in a wealth of knowledge about the genetics and physiology as well as large-scale fermentation characteristics of *Saccharomyces cerevisiae*.

A review of the principles of heterologous gene expression in *Saccharomyces cerevisiae* and secretion of gene products is given by E Hinchcliffe E Kenny (1993, "Yeast as a vehicle for the expression of heterologous genes", Yeasts, Vol 5, Anthony H Rose and J Stuart Harrison, eds, 2nd edition, Academic Press Ltd.).

Several types of yeast vectors are available, including integrative vectors, which require recombination with the host genome for their maintenance, and autonomously replicating plasmid vectors.

In order to prepare the transgenic *Saccharomyces*, expression constructs are prepared by inserting the nucleotide sequence of the present invention into a construct designed for expression in yeast. Several types of constructs used for heterologous expression have been developed. The constructs contain a promoter active in yeast fused to the nucleotide sequence of the present invention, usually a promoter of yeast origin, such as the GAL1 promoter, is used. Usually a signal sequence of yeast origin, such as the sequence encoding the SUC2 signal peptide, is used. A terminator active in yeast ends the expression system.

For the transformation of yeast several transformation protocols have been developed. For example, a transgenic *Saccharomyces* according to the present invention can be prepared by following the teachings of Hinnen et al (1978, Proceedings of the National Academy of Sciences of the USA 75, 1929); Beggs, J D

(1978, Nature, London, 275, 104); and Ito, H et al (1983, J Bacteriology 153, 163-168).

5 The transformed yeast cells are selected using various selective markers. Among the markers used for transformation are a number of auxotrophic markers such as LEU2, HIS4 and TRP1, and dominant antibiotic resistance markers such as aminoglycoside antibiotic markers, eg G418.

10 Another host organism is a plant. The basic principle in the construction of genetically modified plants is to insert genetic information in the plant genome so as to obtain a stable maintenance of the inserted genetic material. Several techniques exist for inserting the genetic information, the two main principles being direct introduction of the genetic information and introduction of the genetic information by use of a vector system. A review of the general techniques may be found in articles
15 by Potrykus (Annu Rev Plant Physiol Plant Mol Biol [1991] 42:205-225) and Christou (Agro-Food-Industry Hi-Tech March/April 1994 17-27). Further teachings on plant transformation may be found in EP-A-0449375.

20 Further hosts suitable for the nucleotide sequence of the present invention include higher eukaryotic cells, such as insect cells or vertebrate cells, particularly mammalian cells, including human cells, or nucleated cells from other multicellular organisms. In recent years propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are epithelial or fibroblastic cell lines such as Chinese hamster ovary (CHO) cells, NIH
25 3T3 cells, HeLa cells or 293T cells.

The nucleotide sequence of the present invention may be stably incorporated into host cells or may be transiently expressed using methods known in the art. By way of example, stably transfected mammalian cells may be prepared by transfecting
30 cells with an expression vector having a selectable marker gene, and growing the transfected cells under conditions selective for cells expressing the marker gene. To prepare transient transfectants, mammalian cells are transfected with a reporter gene to monitor transfection efficiency.

To produce such stably or transiently transfected cells, the cells should be transfected with a sufficient amount of the nucleotide sequence of the present invention. The precise amounts of the nucleotide sequence of the present invention
5 may be empirically determined and optimised for a particular cell and assay.

Thus, the present invention also provides a method of transforming a host cell with a nucleotide sequence that is to be the target or is to express the target. Host cells transformed with the nucleotide sequence may be cultured under conditions suitable
10 for the expression of the encoded protein. The protein produced by a recombinant cell may be displayed on the surface of the cell. If desired, and as will be understood by those of skill in the art, expression vectors containing coding sequences can be designed with signal sequences which direct secretion of the coding sequences through a particular prokaryotic or eukaryotic cell membrane. Other recombinant
15 constructions may join the coding sequence to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins (Kroll DJ et al (1993) DNA Cell Biol 12:441-53).

AGENT

The agent may be an organic compound or other chemical. The agent can be an amino acid sequence or a chemical derivative thereof, or a combination thereof. The agent may even be a nucleotide sequence - which may be a sense sequence or an anti-sense sequence. The agent may even be an antibody.

Typically, the agents will be organic compounds. Typically the organic compounds will comprise two or more hydrocarbyl groups. Here, the term "hydrocarbyl group" means a group comprising at least C and H and may optionally comprise one or more other suitable substituents. Examples of such substituents may include halo-, alkoxy-, nitro-, an alkyl group, a cyclic group etc. In addition to the possibility of the substituents being a cyclic group, a combination of substituents may form a cyclic group. If the hydrocarbyl group comprises more than one C then those carbons need not necessarily be linked to each other. For example, at least two of the carbons may be linked *via* a suitable element or group. Thus, the hydrocarbyl group may contain hetero atoms. Suitable hetero atoms will be apparent to those skilled in the art and include, for instance, sulphur, nitrogen and oxygen. For some applications, preferably the agent comprises at least one cyclic group. The cyclic group may be a polycyclic group, such as a non-fused polycyclic group. For some applications, the agent comprises at least the one of said cyclic groups linked to another hydrocarbyl group.

Examples of agents may be the compounds disclosed in GB patent application No. 9921375.3 (filed 10 September 1999). The teachings of that patent application are annexed hereto (after the Sequence Listings). For ease of reference, the pages of this application (which are numbered 1 etc.) bear the Header "P60162". For the avoidance of doubt, the teachings of that application are also a part of this application.

THERAPY

The agents identified by the assay method of the present invention may be used as
5 therapeutic agents – i.e. in therapy applications.

The term “therapy” includes curative effects, alleviation effects, and prophylactic effects.

10 The therapy may be on humans or animals.

If any agent(s) adversely modulate the CCR5/gp120 interaction, then those agent(s) may be useful in the treatment of anti-inflammatory diseases and conditions and in the treatment and prevention of HIV-1 and genetically related retroviral infections.

15

HIV

In one aspect of the present invention, the assay method is used to identify agents that could be used to treat or prevent the spread or onset of a retroviral infection, especially human immunodeficiency virus (HIV) infection – i.e. treating or preventing
20 HIV infection – and/or as treating or preventing AIDS.

The expressions “treating or preventing AIDS”, and “preventing or treating infection by HIV” as used herein are intended to mean the treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. The quoted expressions are not intended, however, to be limited to the recited treatments, but rather are contemplated to include all beneficial uses relating to conditions attributable to an AIDS causative agent. For example, the identified agents may be useful in treating
25 infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, sexual intercourse, bites, needle stick, or exposure to patient blood. In addition, an identified agent may be used for the prevention of infection by HIV and the prevention of AIDS, such as in pre-or post-coital prophylaxis or in the prevention of maternal transmission of the HIV virus to a fetus or a child, whether at the time of birth, during the period of nursing, or in any
30 other manner.

35

With respect to the spread of HIV infection, it has been shown that for entry into target cells, human immunodeficiency viruses require a chemokine receptor, CCR5 and CXCR-4 among others, as well as the virus's primary receptor CD4. The principal cofactor for entry mediated by the envelope glycoproteins of primary
5 macrophage-tropic strains of HIV-1 is CCR5. Deng, et al., *Nature*, 381, 661-666 (1996) further discuss aspects of CCR5 mediated HIV entry.

In short, HIV attaches to the CD4 molecule on cells through a region of its envelope protein, gp120, and gp120 is part of a multi-subunit complex, most likely a trimer of
10 gp160, i.e., gp120 + gp41. It is believed that the CD4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, triggering conformational changes across the trimer, which allow it to bind to another cell-surface receptor, such as CCR5. This in turn enables gp41 to induce fusion with the cell membrane, and entry of the viral core into the cell. In addition, macrophage-tropic HIV and SIV
15 envelope proteins have been shown to induce a signal through CCR5 on CD4+ cells, which may enhance the replication of the virus. See Weissman, et al., *Nature*, 389, 981-985 (1997) for a description of this phenomenon. Further, it has been shown that a complex of gp120 and soluble CD4 interacts specifically with CCR5 and inhibits the binding of the natural CCR5 ligands, as described in Wu, et al., *Nature*,
20 384, 179-183 (1996); and Trkola, et al., *Nature*, 384, 184-187 (1996). It has further been demonstrated that β -chemokines and related molecules, e.g., (AOP)-RANTES, prevent HIV fusion to the cell membrane and subsequent infection, both in vitro, as described in Dragic, et al., *Nature*, 381, 667-673 (1996), and in animal models. Finally, absence of CCR5 appears to confer protection from HIV-1 infection, as
25 described in *Nature*, 382, 668-669 (1996). In particular, an inherited frame-shifting mutation in the CCR5 gene has been shown to abolish functional expression of the gene in vitro, and individuals homozygous for the mutation are apparently not susceptible to HIV infection, while at the same time they do not seem to be immuno-compromised by this variant. Furthermore, those heterozygote individuals that have
30 been infected by HIV progress more slowly to full-blown clinical AIDS. In addition to validating the role of CCR5 in the infectious cycle of HIV, the above observations suggest that CCR5 is dispensable in the adult organism.

Although most HIV-1 isolates studied to date utilize CCR5 or CXCR-4, at least nine
35 other chemokine receptors, or structurally related molecules, have also been described as supporting HIV-1 env-mediated membrane fusion or viral entry in vitro. These include CCR2b, CCR3, BOB/GPR15, Bonzo/STRL33/TYMSTR, GPR1,

CCR8, US28, V28/CX3CR1, LTB-4, and APJ. There is good evidence that CCR3 can be used efficiently by a significant fraction of HIV-1 isolates in vitro, provided that this protein is over-expressed in transfected cells. Nevertheless, consistent evidence indicates that anti-HIV drugs targeted to chemokine receptors may not be compromised by this variability. Indeed, the chemokines RANTES, MIP-1 α , SDF-1 have been shown to suppress replication of primary HIV isolates. A derivative of RANTES, (AOP)-RANTES, is a sub-nanomolar antagonist of CCR5 function in monocytes. Monoclonal antibodies to CCR5 have been reported to block infection of cells by HIV in vitro. A small molecule antagonist of CXCR4, identified as AMD3100, has been reported to inhibit infection of susceptible cultures by CXCR4 dependent primary and lab-adapted HIV viruses while another small molecule called TAK 779 blocks entry of CCR5-tropic strains (Baba, et al. PNAS, 96 (10), 5698-5703 (1999); In addition, the majority of primary strains from early and late disease stages utilize CCR5 exclusively or in addition to other chemokine receptors, indicating that CCR5 dependent infection may play an essential role in the initiation and maintenance of productive HIV infection in a host. Accordingly, an agent which blocks or adversely modulates CCR5 in patients including mammals, and especially humans who possess normal chemokine receptors, can reasonably be expected to prevent infection in healthy individuals and slow or halt viral progression in infected patients.

ADDITIONAL BIOLOGICAL STUDIES

If desired, the agents identified by the assay method of the present invention can be further investigated using other assay systems.

By way of example, reference may be made to the CCR5 binding assay procedures disclosed in Combadiere et al., J. Leukoc. Biol. 60, 147-52 (1996); and/or intracellular calcium mobilisation assays as described by the same authors. Cell lines expressing the receptor of interest include those naturally expressing the receptor, such as PM-1, or IL-2 stimulated peripheral blood lymphocytes (PBL), or a cell engineered to express a recombinant receptor, such as CHO, 300.19, L1.2 or HEK-293. In particular, the agents may be further investigated to see if they can prevent the binding of further known chemokine ligands to CCR5. In addition, the agents may be studied further to see if they prevent intracellular calcium mobilization in response to endogenous agonists, which is consistent with their functioning as CCR5 antagonists.

Further examples of other assays include those the HIV microculture assays described in Dimitrov et al., J. Clin. Microbiol. 28, 734-737 (1990)), and the pseudotyped HIV reporter assay described in Connor et al., Virology 206 (2) 935-44 (1995). In particular, the agents can be investigated to see if they inhibit p24
5 production following replication of laboratory-adapted and primary HIV strains in primary blood lymphocytes (PBLs) and clonal cell-lines known to support replication of both CCR5 and CXCR-4 tropic viruses, e.g., PM-1 and MOLT4-clone 8. Furthermore, the agents can be investigated to see if they inhibit entry of chimeric HIV reporter viruses pseudotyped with envelope from a CCR5 dependent strain
10 (ADA). Furthermore, the agents can be investigated to see if they inhibit infection of primary cells by HIV isolated from infected patient blood.

PHARMACEUTICAL COMPOSITIONS

15 The present invention also provides a pharmaceutical composition comprising administering a therapeutically effective amount of the agent of the present invention and a pharmaceutically acceptable carrier, diluent or excipients (including combinations thereof).

20 The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine and will typically comprise any one or more of a pharmaceutically acceptable diluent, carrier, or excipient. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R.
25 Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as - or in addition to - the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s).

30 Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

35 There may be different composition/formulation requirements dependent on the different delivery systems. By way of example, the pharmaceutical composition of

the present invention may be formulated to be delivered using a mini-pump or by a mucosal route, for example, as a nasal spray or aerosol for inhalation or ingestible solution, or parenterally in which the composition is formulated by an injectable form, for delivery, by, for example, an intravenous, intramuscular or subcutaneous route. Alternatively, the formulation may be designed to be delivered by both routes.

Where the agent is to be delivered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit through the gastrointestinal tract; for example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile.

Where appropriate, the pharmaceutical compositions can be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents, or they can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parenteral administration, the compositions may be best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood. For buccal or sublingual administration the compositions may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

PHARMACEUTICAL COMBINATIONS

The agent of the present invention may be administered with one or more other pharmaceutically active substances. By way of example, the present invention covers the simultaneous, or sequential treatments with an agent according to the present invention and one or more inhibitors of HIV protease and/or inhibitors of HIV reverse transcriptase, preferably selected from the class of non-nucleoside reverse transcriptase inhibitors (NNRTI), including but not limited to nevirapine, delavirdine, and efavirenz; from among the nucleoside/nucleotide inhibitors, including but not limited to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and adefovir dipivoxil; and from among the protease inhibitors, including but not limited to indinavir, ritonavir, saquinavir, nelfinavir, and amprenavir. Other agents useful in the above-described preferred embodiment combinations of the present invention

include current and to-be-discovered investigational drugs from any of the above classes of inhibitors, including but not limited to FTC, PMPA, fozivudine tidoxil, talviraline, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, and KNI-764.

5

There is also included within the scope of the preferred embodiments of the present invention, combinations of an agent according to the present invention together with a supplementary therapeutic agent used for the purpose of auxiliary treatment, wherein said supplementary therapeutic agent comprises one or more members
10 independently selected from the group consisting of proliferation inhibitors, e.g., hydroxyurea; immunomodulators, e.g., sargramostim, and various forms of interferon or interferon derivatives; fusion inhibitors, e.g., AMD3100, T-20, PRO-542, AD-349, BB-10010 and other chemokine receptor agonists/antagonists; integrase inhibitors, e.g., AR177; RNaseH inhibitors; inhibitors of viral transcription and RNA replication;
15 and other agents that inhibit viral infection or improve the condition or outcome of HIV-infected individuals through different mechanisms.

For some applications, preferred methods of treatment of the present invention for the prevention of HIV infection, or treatment of aviremic and asymptomatic subjects
20 potentially or effectively infected with HIV, include but are not limited to administration of a member independently selected from the group consisting of: (i) an agent according to the present invention; (ii) one NNRTI in addition to a compound of (i); (iii) two NRTI in addition to a compound of (i); (iv) one NRTI in addition to the combination of (ii); and (v) a compound selected from the class of protease inhibitors
25 used in place of an NRTI in combinations (iii) and (iv).

For some applications, preferred methods of treatment of the present invention for the therapy of HIV-infected individuals with detectable viremia or abnormally low CD4 counts further include as a member to be selected: (vi) treatment according to (i)
30 above in addition to the standard recommended initial regimens for the therapy of established HIV infections, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0. Such standard regimens include but are not limited to an agent from the class of protease inhibitors in combination with two NRTIs; and (vii) a standard
35 recommended initial regimens for the therapy of established HIV infections, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0), where either the protease

inhibitor component, or one or both of the NRTIs is/are replaced by an agent according to the present invention.

For some applications, preferred methods of treatment of the present invention for the therapy of HIV-infected individuals that have failed antiviral therapy further include as a member to be selected: (viii) treatment according to (i) above, in addition to the standard recommended regimens for the therapy of such patients, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0); and (ix) a standard recommended initial regimens for the therapy of patients who have failed antiretroviral therapy, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0), where either one of the protease inhibitor components, or one or both of the NRTIs is/are replaced by an agent according to the present invention.

In the above-described combinations of the present invention, the agent of the present invention and other therapeutic active agents may be administered in terms of dosage forms either separately or in conjunction with each other, and in terms of their time of administration, either serially or simultaneously. Thus, the administration of one component agent may be prior to, concurrent with, or subsequent to the administration of the other component agent(s).

ADMINISTRATION

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject and it will vary with the age, weight and response of the particular patient. The dosages below are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited.

The compositions of the present invention may be administered by direct injection. The composition may be formulated for parenteral, mucosal, intramuscular, intravenous, subcutaneous, intraocular or transdermal administration. Depending upon the need, the agent may be administered at a dose of from 0.01 to 30 mg/kg body weight, such as from 0.1 to 10 mg/kg, more preferably from 0.1 to 1 mg/kg body weight.

By way of further example, the agents of the present invention may be administered in accordance with a regimen of 1 to 4 times per day, preferably once or twice per day. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. In particular, however, the treatment of retroviral infections, and more particularly HIV, may be guided by genotyping and phenotyping the virus in the course of or prior to the initiation of administration of the therapeutic agent. In this way, it is possible to optimise dosing regimens and efficacy when administering an agent according to the present invention for the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV).

The term "administered" includes delivery by viral or non-viral techniques. Viral delivery mechanisms include but are not limited to adenoviral vectors, adeno-associated viral (AAV) vectors, herpes viral vectors, retroviral vectors, lentiviral vectors, and baculoviral vectors. Non-viral delivery mechanisms include lipid mediated transfection, liposomes, immunoliposomes, lipofectin, cationic facial amphiphiles (CFAs) and combinations thereof. The routes for such delivery mechanisms include but are not limited to mucosal, nasal, oral, parenteral, gastrointestinal, topical, or sublingual routes.

The term "administered" includes but is not limited to delivery by a mucosal route, for example, as a nasal spray or aerosol for inhalation or as an ingestible solution; a parenteral route where delivery is by an injectable form, such as, for example, an intravenous, intramuscular or subcutaneous route.

For some applications, preferably the agent is administered orally.

GENERAL RECOMBINANT DNA METHODOLOGY TECHNIQUES

Although in general the techniques mentioned herein are well known in the art, reference may be made in particular to Sambrook et al., Molecular Cloning, A Laboratory Manual (1989) and Ausubel et al., Short Protocols in Molecular Biology (1999) 4th Ed, John Wiley & Sons, Inc. PCR is described in US-A-4683195, US-A-

4800195 and US-A-4965188.

SUMMARY

5 Thus, in summary, the present invention provides an assay method for determining whether an agent is capable of modulating the interaction of CCR5 with gp120. The assay method comprises incubating the agent with CCR5 and gp120 to form a first reaction mixture; and determining whether said agent modulates the interaction of CCR5 with gp120. In the method, gp120 is associated with CD4. In particular, in the
10 assay method the interaction of CCR5 with gp120 is a low affinity binding.

The present invention also relates to agents identified using said method, as well as pharmaceutical compositions comprising same, as well as methods of therapy using same.

15

In a preferred embodiment the present invention provides an assay method for determining whether an agent is capable of modulating the interaction of CCR5 with gp120; the method comprising: incubating the agent with CCR5 and gp120 to form a first reaction mixture; and determining whether said agent modulates the interaction
20 of CCR5 with gp120; wherein said gp120 is associated with CD4; wherein said interaction is a low affinity binding; and wherein said method includes the step of adding a ligand to said first reaction mixture to form a second reaction mixture; wherein said ligand is capable of indicating whether said agent has modulated said interaction; and wherein said ligand has a detectable label.

25

In a highly preferred embodiment the present invention provides an assay method for determining whether an agent is capable of modulating the interaction of CCR5 with gp120; the method comprising: incubating the agent with CCR5 and gp120 to form a first reaction mixture; and determining whether said agent modulates the interaction
30 of CCR5 with gp120; wherein said gp120 is associated with CD4; wherein said interaction is a low affinity binding; and wherein said method includes the step of adding a ligand to said first reaction mixture to form a second reaction mixture; wherein said ligand is capable of indicating whether said agent has modulated said interaction; wherein said ligand has a detectable label; and wherein said ligand
35 comprises at least a first antibody, wherein said first antibody is capable of binding to gp120 and wherein said binding is high affinity binding; and wherein said ligand possibly comprises a second antibody, wherein said second antibody is capable of

binding to said first antibody; and wherein said detectable label is associated with said second antibody, or with first antibody if second antibody is not required.

EXAMPLES

The present invention will now be described, by way of example only.

In accordance with the present invention, TR-FIA (time resolved fluorescence immunoassay) is used to determine IC₅₀ of inhibition of gp120 binding to the receptor CCR-5 on MIP34.10 in 96 well plates.

The principle of this assay is based on competitive inhibition of gp120 binding to the receptor CCR-5 on transformed HEK-293 MIP34.10 cells. Varying concentrations of compounds and chemokines are incubated with a constant amount of the gp120, prior to addition of an anti-gp120 antibody and a secondary Eu³⁺ labelled anti-IgG. The displacement of the gp120/CD4 /antibody/antibody complex is measured by time resolved fluorescence (TRF) in a DELFIA Counter and % inhibitions are calculated using XL software.

MATERIALS AND METHODS :

Cell Culture

MIP34.10 cells supplied by Cell Biology and continued passage within the laboratory. PBS (Dulbecco's) without Ca²⁺ and Mg²⁺ - HyQ Reagents,HyClone (cat no : B-4004-L)
1x Cell Dissociation Solution non-enzymatic - Sigma (cat no : C-5914)

Growth medium

500ml 1x Dulbecco's Modified Eagle's Medium (DMEM) with 3.7g/l sodium bicarbonate without L-glutamine - HyQ Reagents, HyClone (cat no : B-7501-L)
50ml foetal calf serum (FCS) - PAA Laboratories, Austria (cat no : A15-041)
5ml 200mM L-Glutamine - Gibco BRL (cat no : 25030-024)
5ml Penicillin/Streptomycin (100U/ml Pen/10mg/ml Strep) - Sigma (cat no : P-7539)
6.5ml 50mg/ml Geneticin - Gibco BRL (cat no : 10131-019)

162cm² Cell Culture Flask Tissue Culture Treated - Costar (cat no : 3151)

Incubator set @ 37°C, 5% CO₂ humidified

Labelling reagents

5

Labelling Buffer :

50mM NaHCO₃ pH 8.5 - Sigma (cat no : S6014)

0.9% NaCl - Sigma (cat no : S5150)

10 Elution Buffer :

50mM Tris-HCl pH 7.8 - Sigma (cat no : T2913)

0.9% NaCl - Sigma (cat no : S5150)

0.05% NaN₃ - Sigma (cat no : S8032)

15 Donkey anti-sheep IgG - Sigma (cat no: S2763)

Delfia Eu-labelling kit - EG&G Wallac (cat no : 1244-302)

PD-10 Sephadex G-25 pre-packed columns - Amersham Pharmacia (cat no : 17-0851-01)

UV detector and tubing

20 Collection tubes

Spectrophotometer

Assay Reagents

25 Dilution / Wash 1 / Assay Buffer :

500ml 1x Dulbecco's Modified Eagle's Medium (DMEM) with 3.7g/l sodium bicarbonate without L-glutamine - HyQ Reagents, HyClone (cat no : B-7501-L)

50ml foetal calf serum (FCS) - PAA Laboratories, Austria (cat no : A15-041)

30 Wash 2 Buffers :

1) Wash concentrate (x25) - EG&G Wallac (cat no : 1380-0865/R)

dilute 1:25 with double distilled water

Dulbecco's PBS - Gibco BRL (cat no : 14190-094)

35

Enhancement

Enhancement solution - EG&G Wallac (cat no : 1244-104)

- sCD4 (human recombinant T-cell) - ImmunoDiagnostics Inc (cat no : 7001)
M-Tropic BaL sgp120 produced in-house
Sheep anti-HIV-1 gp120 antibody (anti C terminal) - Aalto Bio Reagents Ltd, Ireland
5 (cat no : D7324)
Eu3+ labelled donkey anti-sheep IgG - produced in-house as below
MIP-1 a, b or RANTES - R & D Systems (cat no : 270-LD-010, 271-BM-010 and 278-RN-010)
DMSO tissue culture grade - Sigma (cat no : D-2650)
10 Biocoat Cell Environments Poly-D-Lysine 96-well black/clear plates - Becton Dickinson (cat no : 6640)
Haemocytometer Counting Chamber
Multichannel Pipettes - Labsystems Finnpipette (cat no : 4510-000/020/030/040/050)
Pipette Tips - Radleys ABT Aerosol Barrier Tips (cat no : ABT-20/100/2000/1000)
15 Reagent Reservoirs for multichannel pipettes - Costar (cat no : 4870)
DELFI Fluorometer (cat no : 1234-001)

Procedure

20 Cell Culture

MIP34.10 cells supplied by Cell Biology are cultured in 162cm² cell culture flasks to a confluency between 50-70% in the above growth medium @ 37°C for 2-3 days in the humidified incubator.

25

The cells are grown at low density because of their clumpy nature and a tendency to lose their receptor at full confluency.

30

For cell passage, 5ml of cell dissociation solution (non-enzymatic) is added to a 1x washed (PBS) 162cm² flask of cells, the flask rapped on the side to dislodge the cells and split according to usage, usually 1:5 or 1:10 will give sufficient cells for use within 2 -4 days.

35

Each 162cm² flask used for the TR-FIA assay is washed once in 20ml PBS and 5ml cell dissociation solution (non-enzymatic) added, the flask is again rapped on the side to dislodge the cells.

The cells are placed into a 50ml centrifuge tube and 10-20ml assay buffer¹ (care should be taken not to overdilute or the cells will need to be spun down and resuspended in a smaller volume) is added into the flask to wash any residual cells out and then combined in the centrifuge tube.

5

The cells are gently shaken and then counted in a haemocytometer (do appropriate dilutions to enable a count).

10

Dilute the cells to a density of 1×10^6 cells/ml and plate 100µl into every well of the poly-D-Lysine plates and incubate overnight @ 37°C in the humidified incubator.

Eu³⁺ Antibody Preparation

15

Add 500µl of labelling buffer to the anti-sheep IgG to solubilize and transfer to the Eu-labelling reagent vial, mix thoroughly and incubate overnight at 28°C

20

To purify, equilibrate a PD-10 column with 3x the void volume of elution buffer, add the reaction mix and rinse the labelling vial with a small volume of elution buffer and elute.

Monitor the eluate by UV absorbance at 280nm, collect 1-2ml fractions.

Pool the protein peak fractions and measure the Eu³⁺ concentration.

25

Eu³⁺ Content : serially dilute above with enhancement solution from kit (1E-04 - 1E-06) and compare to the fluorescence of 1nM Eu³⁺ standard supplied in the kit.

Protein Content : calculated from the measured absorbance at 280nm after subtracting the absorbance of the formed aromatic thiourea bonds.

30

Calculations

$$\text{Eu}^{3+} \text{ mM} = (\text{Eu counts} \times \text{dilution factor}) / (1000 \times \text{counts of Eu standard})$$

$$\text{Protein mg/ml} = (\text{Abs (280)} - 0.008 \times \text{Eu mM}) / 1.34$$

35

$$\text{Protein mM} = (\text{protein mg/ml} \times 1000000) / 160000$$

Yield = Eu mM / protein mM

Recovery = $100 \times \text{protein mg/ml} \times \text{volume of fraction ml} / \text{protein added mg}$

5 Compound Preparation

Solubilize 1mg compound in DMSO to a final concentration of 10mM.

2) Mix well to solubilize compound, Vortex for 10 seconds or sonibath for 2-5 minutes
10 if necessary. Make a record of compound solubility.

Prepare a dilution series in assay buffer as necessary down at least 6 dilutions
(recommended starting concn of 1(M).

15 Chemokines, if used. MIP-1 a, MIP-1 b and RANTES are prepared in assay buffer
alone. These are sticky proteins and care must be taken on preparing these. 10(g of
lyophilised material is resuspended to give a final concentration of 10(M (sonibath for
2 minutes) and dilution series prepared from this from 200nM down 6 three-fold
dilutions. SP3 special tips are used for all dilutions (ABT aerosol barrier - see assay
20 reagents above).

Assay Protocol

25 Add an equal mix of 36nM sCD4 (100mg/ml solution diluted 1/40 in assay buffer) and
60nM gp120 (1/120 of 1mg/ml) and incubate on ice for 15 minutes.

2) Wash the overnight plates in 100(l wash 1 buffer/well once.

30 Add 20(l compound or control chemokine except for the background control which is
replaced with 40(l assay buffer.

Add 20(l gp120 to each background control well and add 40(l of the sCD4/gp120
complex to each well with compound and reaction control except for the background
control wells.

35

Each mixture contains :

Reaction control : 20(l assay buffer
40(l gp120/sCD4 complex

5 Compound reaction : 20(l compound dilution
40(l gp120/sCD4 complex

Standard reaction : 20(l MIP-1 a, MIP-1 b or RANTES dilution
40(l gp120/sCD4 complex

10 Background control : 40(l binding buffer
20(l gp120

Incubate the 96 well plates @37(C on a rocking platform for 60 minutes.

15 Empty the plate, blot and wash with 100(l/well wash 1 buffer once.

7) Add 100(l/well of a 1/50 dilution of the sheep anti-HIV-1 gp120 antibody to each well and incubate @RT for 90 minutes with rocking.

20 8) Empty the plate, blot and wash with 100(l/well wash 1 buffer once.

9) Add 100(l/well of a 1/1000 dilution of the Eu3+ labelled donkey anti-sheep IgG antibody to each well and incubate @RT for 15 minutes with rocking.

25 10) Empty the plate, blot and wash with 100(l/well wash 2 buffer once.

Empty the plate, blot and wash with 100(l/well PBS buffer 2x.

30 12) Empty the plate, blot and add 200(l/well enhancement solution and vortex for 2-3 minutes.

13) The plates are read in a DELFIA 1234 Fluorometer, plates should be read between 15 and 60 minutes.

Data Analysis

All calculations are performed in Microsoft Excel or Genesis (Lab Systems version
5 2.12).

1) Averages and standard deviations of the replicates are computed, along with CVs.

5) An IC₅₀ value is generated by a four point logistic sigmoid curve fit using XL
10 software.

COMPOUNDS TESTED

Compounds of the type described above were tested in accordance with the present
15 invention and were found to be effective in accordance with the present invention –
i.e. they can modulate the interaction of CCR5 with gp120. In addition, we found that
activity in the described assay correlates well with potency against HIV in
microculture assays referenced above.

20
All publications mentioned in the above specification are herein incorporated by
25 reference. Various modifications and variations of the described methods and system
of the present invention will be apparent to those skilled in the art without departing
from the scope and spirit of the present invention. Although the present invention
has been described in connection with specific preferred embodiments, it should be
understood that the invention as claimed should not be unduly limited to such specific
30 embodiments. Indeed, various modifications of the described modes for carrying out
the invention which are obvious to those skilled in biochemistry and biotechnology or
related fields are intended to be within the scope of the following claims.

REFERENCES FOR CCR5 SECTION

- Alkhatib, G.; Combadiere, C.; Broder, C. C.; Feng, Y.; Kennedy, P. E.; Murphy, P. M.; Berger, E. A. :
5 CC CCR5: a RANTES, MIP-1- α , MIP-1- β receptor as a fusion cofactor for macrophage-tropic HIV-1.
Science 272: 1955-1958, 1996.
- Alvarez, V.; Lopez-Larrea, C.; Coto, E. : Mutational analysis of the CCR5 and CXCR4 genes (HIV-1
co-receptors) in resistance to HIV-1 infection and AIDS development among intravenous drug users.
10 Hum. Genet. 102: 483-486, 1998.
- Ansari-Lari, M. A.; Liu, X.-M.; Metzker, M. L.; Rut, A. R.; Gibbs, R. A. : The extent of genetic
variation in the CCR5 gene. (Letter) Nature Genet. 16: 221-222, 1997.
- 15 Biti, R.; Ffrench, R.; Young, J.; Bennetts, B.; Stewart, G.; Liang, T. : HIV-1 infection in an individual
homozygous for the CCR5 deletion allele. (Letter) Nature Med. 3: 252-253, 1997.
- Browning, J.; Horner, J. W.; Pettoello-Mantovani, M.; Raker, C.; Yurasov, S.; DePinho, R. A.;
Goldstein, H. : Mice transgenic for human CD4 and CCR5 are susceptible to HIV infection. Proc. Nat.
20 Acad. Sci. 94: 14637-14641, 1997.
- Carrington, M.; Dean, M.; Martin, M. P.; O'Brien, S. J. : Genetics of HIV-1 infection: chemokine
receptor CCR5 polymorphism and its consequences. Hum. Molec. Genet. 8: 1939-1945, 1999.
- 25 Choe, H.; Farzan, M.; Sun, Y.; Sullivan, N.; Rollins, B.; Ponath, P. D.; Wu, L.; Mackay, C. R.; LaRosa,
G.; Newman, W.; Gerard, N.; Gerard, C.; Sodroski, J. : The β -chemokine receptors CCR3 and CCR5
facilitate infection by primary HIV-1 isolates. Cell 85: 1135-1148, 1996.
- Cohen, O. J.; Vaccarezza, M.; Lam, G. K.; Baird, B. F.; Wildt, K.; Murphy, P. M.; Zimmerman, P. A.;
30 Nutman, T. B.; Fox, C. H.; Hoover, S.; Adelsberger, J.; Baseler, M.; and 14 others : Heterozygosity for
a defective gene in CC chemokine receptor 5 is not the sole determinant for the immunologic and
virologic phenotype of HIV-infected long-term nonprogressors. J. Clin. Invest. 100: 1581-1589, 1997.
- Dean, M.; Carrington, M.; Winkler, C.; Huttley, G. A.; Smith, M. W.; Allikmets, R.; Goedert, J. J.;
35 Buchbinder, S. P.; Vittinghoff, E.; Gomperts, E.; Donfield, S.; Vlahov, D.; Kaslow, R.; Saah, A.;
Rinaldo, C.; Detels, R.; Hemophilia Growth and Development Study; Multicenter AIDS Cohort Study;
Multicenter Hemophilia Cohort Study; San Francisco City Cohort; ALIVE Study; O'Brien, S. J. :
Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CCR5
structural gene. Science 273: 1856-1861, 1996.

- Deng, H.; Liu, R.; Ellmeier, W.; Choe, S.; Unutmaz, D.; Burkhart, M.; Di Marzio, P.; Marmon, S.; Sutton, R. E.; Hill, C. M.; Davis, C. B.; Peiper, S. C.; Schall, T. J.; Littman, D. R.; Landau, N. R.: Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 381: 661-666, 1996.
- 5 Dragic, T.; Litwin, V.; Allaway, G. P.; Martin, S. R.; Huang, Y.; Nagashima, K. A.; Cayanan, C.; Maddon, P. J.; Koup, R. A.; Moore, J. P.; Paxton, W. A.: HIV-1 entry into CD4(+) cells is mediated by the chemokine receptor CC-CKR-5. *Nature* 381: 667-673, 1996.
- 10 Farzan, M.; Mirzabekov, T.; Kolchinsky, P.; Wyatt, R.; Cayabyab, M.; Gerard, N. P.; Gerard, C.; Sodroski, J.; Choe, H.: Tyrosine sulfation of the amino terminus of CCR5 facilitates HIV-1 entry. *Cell* 96: 667-676, 1999.
- 15 Huang, Y.; Paxton, W. A.; Wolinsky, S. M.; Neumann, A. U.; Zhang, L.; He, T.; Kang, S.; Ceradini, D.; Jin, Z.; Yazdanbakhsh, K.; Kunstman, K.; Erickson, D.; Dragon, E.; Landau, N. R.; Phair, J.; Ho, D. D.; Koup, R. A.: The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. *Nature Med.* 2: 1240-1243, 1996.
- 20 Husain, S.; Goila, R.; Shahi, S.; Banerjee, A. C.: First report of a healthy Indian heterozygous for delta-32 mutant of HIV-1 co-receptor-CCR5 gene. *Gene* 207: 141-147, 1998.
- 25 Libert, F.; Cochaux, P.; Beckman, G.; Samson, M.; Aksenova, M.; Cao, A.; Czeizel, A.; Claustres, M.; de la Rua, C.; Ferrari, M.; Ferrec, C.; Glover, G.; Grinde, B.; Guran, S.; Kucinkas, V.; Lavinha, J.; Mercier, B.; Ogur, G.; Peltonen, L.; Rosatelli, C.; Schwartz, M.; Spitsyn, V.; Timar, L.; Beckman, L.; Parmentier, M.; Vassart, G.: The delta-CCR5 mutation conferring protection against HIV-1 in Caucasian populations has a single and recent origin in northeastern Europe. *Hum. Molec. Genet.* 7: 399-406, 1998.
- 30 Liu, R.; Paxton, W. A.; Choe, S.; Ceradini, D.; Martin, S. R.; Horuk, R.; MacDonald, M. E.; Stuhlmann, H.; Koup, R. A.; Landau, N. R.: Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* 86: 367-377, 1996.
- 35 Martin, M. P.; Dean, M.; Smith, M. W.; Winkler, C.; Gerrard, B.; Michael, N. L.; Lee, B.; Doms, R. W.; Margolick, J.; Buchbinder, S.; Goedert, J. J.; O'Brien, T. R.; Hilgartner, M. W.; Vlahov, D.; O'Brien, S. J.; Carrington, M.: Genetic acceleration of AIDS progression by a promoter variant of CCR5. *Science* 282: 1907-1911, 1998.
- Martinson, J. J.; Chapman, N. H.; Rees, D. C.; Liu, Y.-T.; Clegg, J. B.: Global distribution of the CCR5 gene 32-basepair deletion. *Nature Genet.* 16: 100-103, 1997.

- McDermott, D. H.; Zimmerman, P. A.; Guignard, F.; Kleeberger, C. A.; Leitman, S. F.; Murphy, P. M. : CCR5 promoter polymorphism and HIV-1 disease progression: multicenter AIDS cohort study (MACS). *Lancet* 352: 866-870, 1998.
- 5 Quillent, C.; Oberlin, E.; Braun, J.; Rousset, D.; Gonzalez-Canali, G.; Metais, P.; Montagnier, L.; Virelizier, J.-L.; Arenzana-Seisdedos, F.; Beretta, A. : HIV-1-resistance phenotype conferred by combination of two separate inherited mutations of CCR5 gene. *Lancet* 351: 14-18, 1998.
- 10 Rottman, J. B.; Ganley, K. P.; Williams, K.; Wu, L.; Mackay, C. R.; Ringler, D. J. : Cellular localization of the chemokine receptor CCR5: correlation to cellular targets of HIV-1 infection. *Am. J. Path.* 151: 1341-1351, 1997.
- 15 Samson, M.; Labbe, O.; Mollereau, C.; Vassart, G.; Parmentier, M. : Molecular cloning and functional expression of a new human CC-chemokine receptor gene. *Biochemistry* 35: 3362-3367, 1996.
- 20 Samson, M.; Libert, F.; Doranz, B. J.; Rucker, J.; Liesnard, C.; Farber, C.-M.; Saragosti, S.; Lapoumeroulie, C.; Cogniaux, J.; Forceille, C.; Muyldermans, G.; Verhofstede, C.; Burtonboy, G.; Georges, M.; Imai, T.; Rana, S.; Yi, Y.; Smyth, R. J.; Collman, R. G.; Doms, R. W.; Vassart, G.; Parmentier, M. : Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* 382: 722-725, 1996.
- 25 Smith, M. W.; Dean, M.; Carrington, M.; Winkler, C.; Huttley, G. A.; Lomb, D. A.; Goedert, J. J.; O'Brien, T. R.; Jacobson, L. P.; Kaslow, R.; Buchbinder, S.; Vittinghoff, E.; Vlahov, D.; Hoots, K.; Hilgartner, M. W.; Hemophilia Growth and Development Study (HGDS); Multicenter AIDS Cohort Study (MACS); Multicenter Hemophilia Cohort Study (MHCS); San Francisco City Cohort (SFCC); ALIVE Study; O'Brien, S. J. : Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. *Science* 277: 959-965, 1997.
- 30 Stephens, J. C.; Reich, D. E.; Goldstein, D. B.; Shin, H. D.; Smith, M. W.; Carrington, M.; Winkler, C.; Huttley, G. A.; Allikmets, R.; Schriml, L.; Gerrard, B.; Malasky, M.; and 27 others : Dating the origin of the CCR5-del32 AIDS-resistance allele by the coalescence of haplotypes. *Am. J. Hum. Genet.* 62: 1507-1515, 1998.
- 35 Zagury, D.; Lachgar, A.; Chams, V.; Fall, L. S.; Bernard, J.; Zagury, J.-F.; Bizzini, B.; Gringeri, A.; Santagostino, E.; Rappaport, J.; Feldman, M.; O'Brien, S. J.; Burny, A.; Gallo, R. C. : C-C chemokines, pivotal in protection against HIV type 1 infection. *Proc. Nat. Acad. Sci.* 95: 3857-3861, 1998.

- Zimmerman, P. A.; Buckler-White, A.; Alkhatib, G.; Spalding, T.; Kubofcik, J.; Combadiere, C.; Weissman, D.; Cohen, O.; Rubbert, A.; Lam, G.; Vaccarezza, M.; Kennedy, P. E.; Kumaraswami, V.; Giorgi, J. V.; Detels, R.; Hunter, J.; Chopek, M.; Berger, E. A.; Fauci, A. S.; Nutman, T. B.; Murphy, P. M. : Inherited resistance to HIV-1 conferred by an inactivating mutation in CC chemokine receptor 5: studies in populations with contrasting clinical phenotypes, defined racial background, and quantified risk. *Molec. Med.* 3: 23-26, 1997.

REFERENCES FOR CD4 SECTION

- 10 Amadori, A.; Zamarchi, R.; De Silvestro, G.; Forza, G.; Cavatton, G.; Danieli, G. A.; Clememti, M.; Chieco-Bianchi, L. : Genetic control of the CD4/CD8 T-cell ratio in humans. *Nature Med.* 1: 1279-1283, 1995.
- 15 Chakravarti, A. : The CD4/CD8 ratio: message in a bottle? *Nature Med.* 1: 1240-1241, 1995.
- Clementi, M.; Forabosco, P.; Amadori, A.; Zamarchi, R.; De Silvestro, G.; Di Gianantonio, E.; Chieco-Bianchi, L.; Tenconi, R. : CD4 and CD8 T lymphocyte inheritance: evidence for major autosomal recessive genes. *Hum. Genet.* 105: 337-342, 1999.
- 20 Kraal, G.; Weissman, I. L.; Butcher, E. C. : Genetic control of T-cell subset representation in inbred mice. *Immunogenetics.* 18: 585-592, 1983.

CLAIMS

1. An assay method for determining whether an agent is capable of modulating
5 the interaction of CCR5 with gp120;

the method comprising:

incubating the agent with CCR5 and gp120 to form a first reaction mixture; and
10 determining whether said agent modulates the interaction of CCR5 with gp120;

wherein said gp120 is associated with CD4; and

15 wherein said interaction is a low affinity binding.
2. A method according to claim 1 wherein said method includes the step of
adding a ligand to said first reaction mixture to form a second reaction mixture;
wherein said ligand is capable of indicating whether said agent has modulated said
20 interaction.
3. A method according to claim 2 wherein said ligand has a detectable label.
4. A method according to claim 3 wherein said detectable label is a fluorescent
25 atom or a fluorescent group.
5. A method according to claim 5 wherein said radioactive atom is Eu^{3+} .
6. A method according to any one of claims 2 to 5 wherein said ligand
30 comprises at least a first antibody.
7. A method according to claim 6 wherein said first antibody is capable of
binding to gp120; and wherein said binding is high affinity binding, preferably wherein
said first antibody is associated with a detectable label.
35
8. A method according to claim 6 or claim 7 wherein said ligand comprises at
least a second antibody.

9. A method according to claim 7 wherein said second antibody is capable of binding to said first antibody.

5 10. A method according to claim 9 wherein said second antibody is an anti-IgG antibody.

11. A method according to any one of claims 8 to 10 when dependent on claim 3 wherein said detectable label is associated with said second antibody.

10

12. An agent identified by the method according to any one of claims 1 to 11, wherein said agent is capable of modulating the interaction of CCR5 with gp120.

13. A process comprising the steps of:

15

(a) performing the assay according to any one of claims 1 to 11;

(b) identifying one or more agents that are capable of modulating the interaction of CCR5 with gp120; and

20

(c) preparing a quantity of those one or more identified agents.

14. A method of affecting the *in vivo* interaction of CCR5 with gp120 with an agent;

25

wherein the agent is capable of modulating the interaction of CCR5 with gp120 in an *in vitro* assay method;

30

wherein the *in vitro* assay method is the assay method defined in any one of claims 1 to 11.

35

15. Use of an agent in the preparation of a pharmaceutical composition for the treatment of a disease or condition associated with the interaction of CCR5 with gp120, wherein the agent is the agent of claim 12 and/or wherein the agent is capable of modulating the interaction of CCR5 with gp120 when assayed *in vitro* by the assay method according to any one of claims 1 to 11.

16. A method of treating a subject with an agent, wherein the agent is the agent of claim 12 and/or wherein the agent is capable of modulating the interaction of CCR5 with gp120 when assayed *in vitro* by the assay method according to any one of claims 1 to 11.

5

10

ABSTRACT**METHOD**

5

An assay method for determining whether an agent is capable of modulating the interaction of CCR5 with gp120 is disclosed. The method comprises incubating the agent with CCR5 and gp120 to form a first reaction mixture; and determining whether said agent modulates the interaction of CCR5 with gp120; wherein said gp120 is associated with CD4. In particular, the interaction is a low affinity binding.

10

SEQUENCE LISTINGS

CCR5

5 ID T90117 standard; cDNA; 1477 BP.
 DE cDNA for human CCR5.
 KW Human Cys-Cys chemokine receptor 5; CCR5; human immunodeficiency virus; type 1; type 2; HIV-1; HIV-2; diagnosis; treatment; prevention; inflammatory disease; rheumatoid arthritis;
 10 glomerulonephritis; asthma; idiopathic pulmonary fibrosis; psoriasis; viral infection; cancer; atherosclerosis; autoimmune disorder; ss.
 OS Homo sapiens.
 FH Key Location/Qualifiers
 FT CDS 240..1298
 15 SQ Sequence 1477 BP; 374 A; 349 C; 320 G; 431 T; 3 other

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45 SQ SEQUENCE 352 AA; 40524 MW; 7E61FEA5 CRC32;
 MDYQVSSPIY DINYYTSEPC QKINVQIAA RLLPLYSLV FIFGFVGNML VILILINCKR
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gp120Gp120 Sequences, HIV-1 BaL strain

5

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30

Amino-acid

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CD4

ID N90764 standard; cDNA; 1113 BP.

5 KW Human soluble CD4 protein; T4 SEC1 cDNA; T4ex1; HIV gp120 envelope protein; T-lymphocyte.

OS Homo sapiens.

FH Key Location/Qualifiers

FT CDS 1..1113

10 FT /*tag= a

FT misc_difference 385..387

FT /*tag= b

FT misc_difference 487..489

FT /*tag= c

15 FT misc_difference 547..549

FT /*tag= d

FT misc_difference 727..729

FT /*tag= e

FT misc_difference 1108..1110

20 FT /*tag= f

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ID P93528 standard; protein; 370 AA.

45 FH Key Location/Qualifiers

FT Misc-difference 129

FT Misc-difference 183

FT Misc-difference 163

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50 FT Misc-difference 370

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SQ 13 I; 48 L; 39 K; 4 M; 10 F; 16 P; 35 S; 25 T; 10 W; 3 Y; 28 V;

SQ 0 Others;

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vlptwstpvh

ANNEX NOW FOLLOWS

CCR5 MODULATORS

This invention relates to new chemical compounds. These compounds find particular but not exclusive use as pharmaceuticals, especially as CCR5 modulators.

5 This invention also relates to formulations or dosage forms including these compounds, to use of these compounds in manufacture of pharmaceutical formulations or dosage forms and methods of treatment, especially treatment of anti-inflammatory diseases and conditions and in the treatment and prevention of HIV-1 and genetically related retroviral infections.

10 The compounds of the present invention may be modulators, especially antagonists, of the activity of chemokine CCR5 receptors, particularly those which occur on the surfaces of certain cells within the human body. Modulators of CCR5 receptor may be useful in the treatment and prevention of various inflammatory diseases and conditions, and in the treatment and prevention of infection by HIV-1 and genetically related retroviruses.

15 The name "chemokine", is a contraction of "chemotactic cytokines". The chemokines comprise a large family of proteins which have in common important structural features and which have the ability to attract leukocytes. As leukocyte chemotactic factors, chemokines play an indispensable role in the attraction of leukocytes to various tissues of the body, a process which is essential for both inflammation and the body's response to infection.
20 Because chemokines and their receptors are central to the pathophysiology of inflammatory and infectious diseases, agents which are active in modulating, preferably antagonizing, the activity of chemokines and their receptors, are useful in the therapeutic treatment of such inflammatory and infectious diseases.

 The chemokine receptor CCR5 is of particular importance in the context of treating
25 inflammatory and infectious diseases. CCR5 is a receptor for chemokines, especially for the macrophage inflammatory proteins (MIP) designated MIP-1 α and MIP-1 β , and for a protein which is regulated upon activation and is normal T-cell expressed and secreted (RANTES). The relationship between modulators, especially antagonists of CCR5 activity and therapeutic usefulness in treating inflammation and HIV infection, and the manner in which such a
30 relationship may be demonstrated, is explained in more detail further below.

 There is ongoing in the art a substantial investigation of different classes of modulators of chemokine receptor activity, especially that of the CCR5 chemokine receptor. A representative disclosure is Mills *et al.* WO 98/25617 relating to substituted aryl piperazines as modulators of chemokine receptor activity. However, the compositions described therein are

not the same as, nor suggestive of those of the present invention. Further disclosures are: WO 98/025605; WO 98/025604; WO 98/002151; WO 98/004554; and WO 97/024325.

The present invention relates to compounds which may be conveniently considered to have four independently variable regions, reading from the left-hand side to right-hand side of said compound: R_{region α}, R_{region β}, R_{region γ}, and R_{region δ}, of Formula (I):



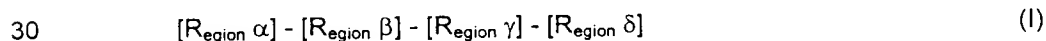
and pharmaceutically acceptable salts and prodrug derivatives thereof. The compounds of the present invention may be selective CCR5 receptor modulators and are non-peptidyl in structure.

The compounds as exemplified by Formula (I) may contain one or more stereogenic centers and the present invention includes the recited compounds in both their separated and their unseparated forms. The separated forms can be obtained by conventional means, e.g., by asymmetric synthesis, by using high performance liquid chromatography employing a chiral stationary phase, or by chemical resolution via the formation of suitable salts or derivatives. It will be understood that the separate optically active forms of the compositions of the present invention, as well as racemic mixtures thereof, will usually vary with respect to their biological properties because of the chirality-dependent conformation of the active site of an enzyme, receptor, etc.

The description which follows provides details of the particular moieties which comprise each of said R_{regions}. In order to present said details in an orderly and space-saving fashion, each major group in each Region is set out with a single dash (" - "), and each successive subdivision within each said group is set out in turn with two, three, etc. dashes as required.

In this specification and claims a reference to a range or class of groups for example (C₁-C₃)alkyl is to be understood as an express disclosure and reference of each member of the range or class, including isomers.

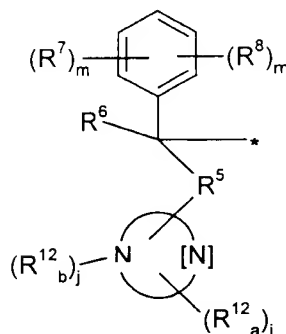
According to the present invention there is provided a compound of Formula (I);



wherein [R_{region α}] is selected from the group consisting of:

-A. Aryl heterocyclyl substituent components comprising:

--1. hetero-phenylmethylene moieties of partial Formula (1.0.0):



(1.0.0)

---wherein: the symbol " * " indicates the point of attachment of the moiety of partial Formula
5 (1.0.0) to $R_{\text{region } \beta}$, as hereinafter defined;

--- R^5 is a member selected from the group consisting of a direct bond; -O-; -C(=O)-; - NR^4 -; and -S(=O)_p-; where:

---- R^4 is hydrogen or (C₁.C₂)alkyl;

--- R^6 is a member selected from the group consisting of hydrogen; (C₁.C₂)alkyl;
10 (C₁.C₂)alkoxy; -CN; -OH; and -C(=O)NH₂;

---j is an integer selected from 0, 1, and 2;

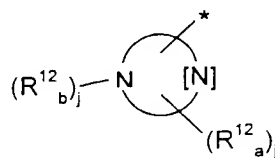
---m is an integer selected from 0, 1, and 2;

--- R^7 and R^8 are each a member selected from the group consisting of -F; -Cl; -CO₂ R^4 ; -OH; -CN; -CONR⁴_a R^4 _b; -NR⁴_a R^4 _b-; -NR⁴_aC(=O) R^4 _b; -NR⁴_aC(=O)OR⁴_b; -NR⁴_aS(=O)_p R^4 _b; -S(=O)_pNR⁴_a R^4 _b; (C₁.C₄)alkyl, and (C₁.C₄)alkoxy wherein said alkyl and alkoxy are each
15 substituted with 0 to 3 substituents independently selected from F and Cl; (C₁.C₂)alkoxycarbonyl; (C₁.C₂)alkylcarbonyl; and (C₁.C₂)alkylcarbonyloxy; where:

----p is an integer selected from 0, 1, and 2;

---- R^4_a and R^4_b are each independently selected from hydrogen and (C₁.C₂)alkyl;

20 ---the moiety represented by partial Formula (1.0.1):



(1.0.1)

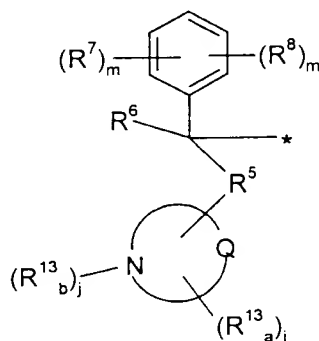
in partial Formula (1.0.0) represents a monocyclic heterocyclic group, or a bicyclic benzo-fused ring system containing said heterocyclic group wherein said heterocyclic group contains a total of 5- or 6- members of which one or two of said members is nitrogen, the presence of the optional second nitrogen atom being represented by: "[N]";
 5 wherein said heterocyclic group or ring system are selected from the group consisting of pyrrolyl; pyrazolyl; imidazolyl; pyridinyl; pyrazinyl; pyrimidinyl; pyridazinyl; piperazinyl; indolyl; indazolyl; benzimidazolyl; quinolyl; *iso*-quinolyl; and quinazolyl; wherein:

10 $---R^{12}_a$ is a member selected from the group consisting of hydrogen; F; Cl; $-CO_2R^4$; oxo; $-OH$; CN; NH_2 ; $NH(C_1-C_2)alkyl$; $N(C_1-C_2)_2dialkyl$; $-CF_3$; $(C_1-C_4)alkyl$; $(C_2-C_4)alkenyl$; $(C_1-C_4)alkoxy$; $(C_3-C_7)cycloalkyl$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^9 where:

15 $----R^9$ is a member independently selected from the group consisting of F; Cl; $-CO_2R^4$; $-OH$; cyano; $-CONR^4_aR^4_b$; $-NR^4_aR^4_b$; $-NR^4_aC(=O)R^4_b$; $-NR^4_aC(=O)OR^4_b$; $-NR^4_aS(=O)_pR^4_b$; $-S(=O)_pNR^4_aR^4_b$; $(C_1-C_4)alkyl$ including dimethyl, and $(C_1-C_4)alkoxy$ wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; $(C_1-C_2)alkoxycarbonyl$; $(C_1-C_2)alkylcarbonyl$; and $(C_1-C_2)alkylcarbonyloxy$; and

20 $----R^{12}_b$ is absent or is a member selected from the group consisting of hydrogen; $(C_1-C_4)alkyl$; $(C_2-C_4)alkenyl$; $(C_1-C_2)alkoxy$; $(C_3-C_7)cycloalkyl$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^9 wherein R^9 has the same meaning as above, except that it is selected independently selected therefrom; and

2. hetero-phenylmethylene moieties of partial Formula (1.1.0):

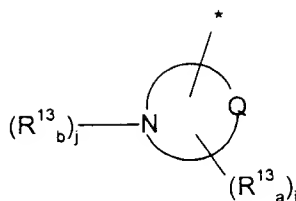


(1.1.0)

25

---wherein: the symbol " * "; R^5 ; R^6 ; R^7 ; R^8 ; j and m are as defined further above, except that all of the above-recited substituents are selected independently of their selection above;

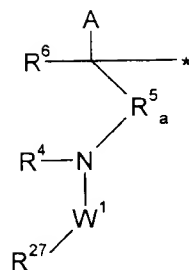
---the moiety represented by partial Formula (1.1.1):



(1.1.1)

in partial Formula (1.1.0) represents:

- 5 ----a. a monocyclic heterocyclic group containing a total of 5 or 6 members of which one said member is nitrogen and Q is selected from O and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; wherein said heterocyclic group is selected from the group consisting of oxazolyl; oxazolidinyl; isoxazolyl; thiazolyl; thiazolidinyl; *iso*-thiazolyl; morpholinyl; and thiomorpholinyl; or
- 10 ----b. a monocyclic heterocyclic group containing a total of 5- or 6- member s of which two said members are nitrogen and a third or fourth said member is independently selected from N, O, and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; wherein said heterocyclic group is selected from the group consisting of triazolyl; triazinyl; tetrazolyl; oxadiazolyl; thiadiazolyl; and
- 15 ---- R^{13}_a is selected from the group consisting of hydrogen; F; Cl; $-CO_2R^4$; oxo; $-OH$; CN; NH_2 ; $NH(C_1-C_2)alkyl$; $N(C_1-C_2)_2dialkyl$; $-CF_3$; $(C_1-C_4)alkyl$; $(C_2-C_4)alkenyl$; $(C_1-C_2)alkoxy$; $(C_3-C_7)cycloalkyl$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^{11} where:
- 20 ---- R^{11} is a member selected from the group consisting of F; Cl; $-CO_2R^4$; $-OH$; $-CN$; $-CONR^4_aR^4_b$; $-NR^4_aR^4_b$; $-NR^4_aC(=O)R^4_b$; $-NR^4_aC(=O)OR^4_b$; $-NR^4_aS(=O)_pR^4_b$; $-S(=O)_pNR^4_aR^4_b$; $(C_1-C_4)alkyl$ including dimethyl, and $(C_1-C_4)alkoxy$ wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; $(C_1-C_2)alkoxycarbonyl$; $(C_1-C_2)alkylcarbonyl$; and $(C_1-C_2)alkylcarbonyloxy$; and
- 25 ---- R^{13}_b is a member selected from the group consisting of hydrogen; $(C_1-C_4)alkyl$; $(C_2-C_4)alkenyl$; $(C_1-C_2)alkoxy$; $(C_3-C_7)cycloalkyl$; $C(=O)(C_1-C_4)alkyl$; $S(=O)_2(C_1-C_4)alkyl$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^{11} wherein R^{11} has the same meaning as in above, except that it is selected independently;
- 30 -B. a (substituted)-amido-aryl or -heterocyclyl moiety selected from the group consisting of --1. alkyl-, alkenyl-, and alkynyl-substituted-amido-aryl moieties of partial Formula (2.0.0):

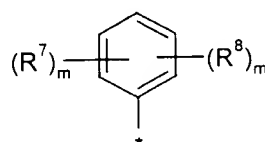


(2.0.0)

---wherein: the symbol " * "; R^4 and R^6 ; are as defined above, except that all of the above-recited substituents are selected independently of their selection above;

5 ---A is a member selected from the group consisting of:

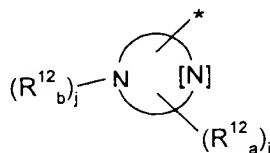
----1. the moiety of partial Formula (2.0.3)



(2.0.3)

10 -----wherein: the symbol R^7 ; R^8 and m are as defined above, except that all of the above-recited substituents are selected independently of their selection above; and the symbol: " * " indicates the point of attachment of the moiety A to the, remaining portions of partial Formula (2.0.0);

----2. the moiety of partial Formula (2.0.4)



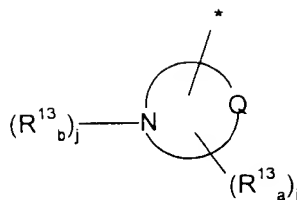
(2.0.4)

15

which represents a monocyclic heterocyclic group, selected from the group consisting of pyrrolyl; pyrazolyl; imidazolyl; pyridinyl; pyrazinyl; pyrimidinyl; wherein: the symbol R^{12}_a and R^{12}_b are as defined above, except that all of the above-recited substituents are selected independently of their selection above; and the symbol: " * " indicates the point of attachment

20 of the moiety A to the other, remaining portions of partial Formula (2.0.0);

----3. the moiety of partial Formula (2.0.5)



(2.0.5)

which represents

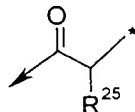
- a. a monocyclic heteroaromatic group containing a total of 5- members of which one
 5 said member is nitrogen and Q is selected from O and S where said S may optionally be
 in the sulfonate form, $-S(=O)_2$; selected from the group consisting of oxazolyl; isoxazolyl;
 thiazolyl; and *iso*-thiazolyl; or
- b. a monocyclic heterocyclic group containing a total of 5- or 6- members of which two
 10 said members are nitrogen and a third or fourth said member is independently selected
 from N, O, and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; selected
 from the group consisting of triazolyl; triazinyl; tetrazolyl; oxadiazolyl; and thiadiazolyl; and
 -----wherein: the R^{13}_a , R^{13}_b and j are as defined above, except that all of the above-
 recited substituents are selected independently of their selection above; and the symbol:
 " * " indicates the point of attachment of the moiety A to the other, remaining portions of
 15 partial Formula (2.0.2);

--- R^5_a is a member selected from the group consisting of a direct bond; $-C(=O)-$; and
 $-S(=O)_2-$;

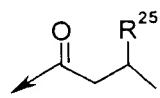
- W^1 is (1.) a direct bond; (2.) in the case where R^5_a is $-C(=O)-$ or $-S(=O)_2$, W^1 is a direct bond
 or $-(C_1-C_3)$ alkylene- wherein any single carbon atom thereof is substituted by 0 to 2
 20 substituents R^{23} where R^{23} is a member selected from the group consisting of $-F$; $-Cl$;
 $-CO_2R^4$; $-OH$; $-CN$; (C_1-C_4) alkoxy; (C_3-C_7) cycloalkyl; and phenyl; wherein said alkoxy,
 cycloalkyl, and phenyl are substituted with 0 to 2 substituents R^{11} , wherein said R^{11} is as
 defined above, except that all of the above-recited substituents are selected independently
 of their selection above; or (3.) is a member independently selected from the group
 25 consisting of the moieties of partial Formulas (2.0.6) through (2.0.16), inclusive:



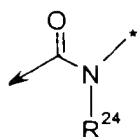
(2.0.6)



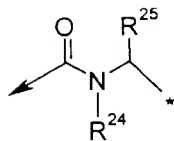
(2.0.7)



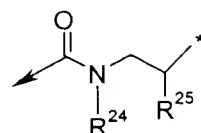
(2.0.8)



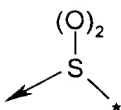
(2.0.9)



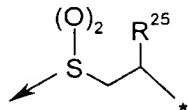
(2.0.10)



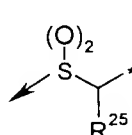
(2.0.11)



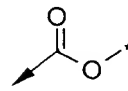
(2.0.12)



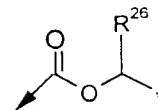
(2.0.13)



(2.0.14)



(2.0.15)



(2.0.16)

- 5 ----wherein: the symbol: "→" indicates the point of attachment of the moiety W¹ to the nitrogen atom in partial Formula (2.0.0), and the symbol: "*" indicates the point of attachment of the moiety W¹ to the other, remaining portions of partial Formula (2.0.0); and R⁴ is as defined further above, but selected on an independent basis;

-----R²⁴ is selected from the group consisting of hydrogen and (C₁-C₄)alkyl; and

- 10 ----R²⁵ and R²⁶ are each selected from the group consisting of -OH; (C₁-C₂)alkyl substituted by 0 to 3 substituents selected from F; and OH; and (C₁-C₂)alkoxy; and

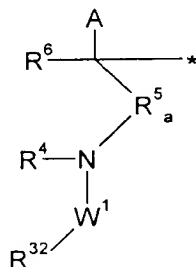
---R²⁷ is selected from the group consisting of (C₁-C₆)alkyl; (C₂-C₆)alkenyl; and (C₂-C₆)alkynyl; wherein said alkyl, alkenyl, and alkynyl groups comprising R²⁷ are substituted with 0 to 3 substituents R²⁸ where:

- 15 ----R²⁸ is selected from the group consisting of phenyl; F or Cl; oxo; hydroxy; (C₁-C₂)alkyl; (C₁-C₃)alkoxy; -C(=O)OR²⁹; -C(=O)(C₁-C₄)alkyl; -S(=O)₂(C₁-C₄)alkyl; -C(=O)NR²⁹R³⁰; -NR²⁹R³⁰; -NR²⁹C(=O)R³⁰; -NR²⁹C(=O)OR³⁰; -NR²⁹S(=O)_pR³⁰; and -S(=O)₂NR²⁹R³⁰, where:

-----R²⁹ and R³⁰ are each a member independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl substituted by 0 to 3 substituents selected from the group consisting of F and Cl;

20

--2. cycloalkyl-substituted-amido-aryl moieties of partial Formula (2.1.0):

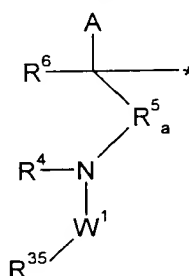


(2.1.0)

---wherein: A; W¹; the symbol " * "; R⁴; R⁵_a; and R⁶ have the same meaning as set out above, except that all of the above-recited substituents are selected independently of their selection above; and

5 ---R³² is a member selected from the group consisting of -(CH₂)_n-(C₃-C₇)cycloalkyl, where n is an integer selected from 0, 1, and 2; in the event n is 0, then the α-carbon atom of said (C₃-C₇)cycloalkyl is substituted by 0 or 1 (C₁-C₄)alkyl or phenyl, where said alkyl or phenyl are substituted by 0, 1, or 2 of CH₃, OCH₃, OH or NH₂; and in the event that n is 1 or 2, the resulting methylene or ethylene is substituted by 0 or 1 of F; NH₂; N(CH₃)₂; OH; OCH₃; (C₁-C₄)alkyl; or phenyl; where said alkyl and phenyl are substituted by 0, 1, or 2 of CH₃, OCH₃, OH, and NH₂; and further wherein said (C₃-C₇)cycloalkyl is substituted by 0 to 3 substituents R²⁸ where R²⁸ is as defined further above, but selected independently

---3. aryl and heterocyclic-substituted-amido-aryl moieties of partial Formula (2.2.0):



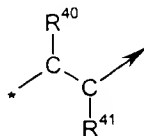
(2.2.0)

15 ---wherein: A; W¹; the symbol: " * "; R⁴; R⁵_a; and R⁶ have the same meaning as set out above, except that all of the above-recited substituents are selected independently of their selection above; and

20 ---R³⁵ is selected from the group consisting of phenyl; furyl; tetrahydrofuranyl; tetrahydropyranyl; oxetanyl; thienyl; pyrrolyl; pyrrolidinyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; imidazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; piperazinyl; pyrimidinyl; pyranyl; azetidiny; morpholiny; parathiazinyl; indolyl; indoliny; benzo[b]furanyl; 2;3-dihydrobenzofuranyl; benzothienyl; 1H-indazolyl; benzimidazolyl; benzoxazolyl; benzisoxazolyl; benzthiazolyl; quinoliny; isoquinoliny; phthalazinyl; quinazoliny; and quinoxaliny; wherein (1.) said group R³⁵ may be substituted upon any one or more carbon atoms thereof by 0 to 3 substituents R²⁸ where R²⁸ is as defined above, except that it is selected independently; (2.) said group R³⁵ is substituted with respect to any one or more nitrogen atoms thereof that is not a point of attachment of said aryl or heterocyclic moiety, by 0 to 3 substituents R¹³_b where R¹³_b is as defined above, except that it is selected independently; and (3.) said group R³⁵ with respect to any sulfur

atom thereof that is not a point of attachment of said heterocyclic moiety, is substituted by 0 or 2 oxygen atoms;

[R_{region β}] is an alkyl bridging element of partial Formula (3.0.0):



(3.0.0)

5

wherein:

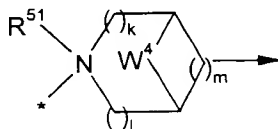
--" * " is a symbol which represents the point of attachment of the moiety of partial Formula (3.0.0) to R_{region α};

--" → " is a symbol which represents the point of attachment of the moiety of partial Formula (3.0.0) to R_{region γ};

10

--R⁴⁰ and R⁴¹ are independently selected from the group consisting of hydrogen; (C₁-C₂) alkyl including dimethyl; hydroxy; and (C₁-C₃) alkoxy;

[R_{region γ}] is an aza-bicyclic moiety of partial Formula (4.2.0):



(4.2.0)

15

--wherein

--" * " is a symbol which represents the point of attachment of the moiety of partial Formula (4.2.0) to R_{region β};

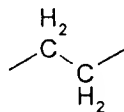
--" → " is a symbol representing a covalent bond from any of the carbon atoms of the moiety of partial Formula (4.2.0) to R_{region δ};

20

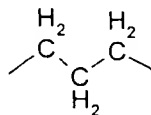
--W⁴ is a direct bond; or is a member independently selected from the group consisting of partial Formulas (4.2.1) through (4.2.6):



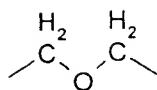
(4.2.1)



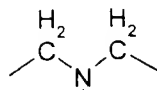
(4.2.2)



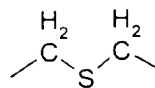
(4.2.3)



(4.2.4)



(4.2.5)



(4.2.6)

---where:

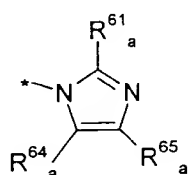
5 ---R⁵² is a member selected from the group consisting of hydrogen; phenyl; (C₁-C₄)alkyl substituted by 0 or 1 substituent independently selected from (C₁-C₂)alkoxy and -CO₂R⁴; (C₃-C₆)cycloalkyl; -CO₂R⁴; →O; C(=O)(C₁-C₃)alkyl; -C(=O)NR⁴_aR⁴_b; -S(=O)(C₁-C₄)alkyl; and (C₁-C₂)alkylcarbonyl; where R⁴, R⁴_a, and R⁴_b are as defined above, but selected on an independent basis;

10 --R⁵¹ is absent or is a member selected from the group consisting of (C₁-C₄)alkyl substituted by 0 or 1 substituent independently selected from (C₁-C₂)alkoxy and -CO₂R⁴ where R⁴ is as defined above; and →O; it being understood that in the case where substituent R⁵¹ is present, the nitrogen atom is in quaternary form; and

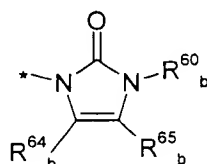
--k, l and m are each an integer selected from 0, 1, 2, and 3;

[R_{egion δ}] is a member selected from the group consisting of:

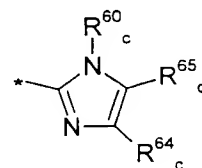
15 -A. a two-nitrogen-atom-containing five-membered heterocyclic moiety of partial Formulas (5.0.0) through (5.0.10):



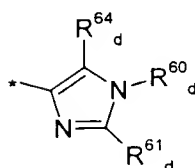
(5.0.0)



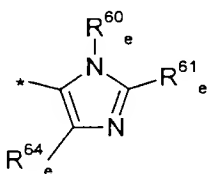
(5.0.1)



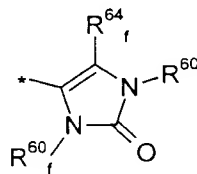
(5.0.2)



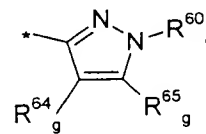
(5.0.3)



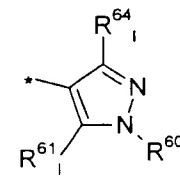
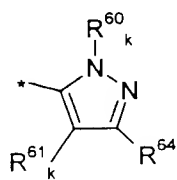
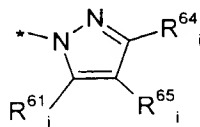
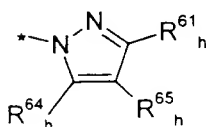
(5.0.4)



(5.0.5)



(5.0.6)



(5.0.7)

(5.0.8)

(5.0.9)

(5.0.10)

--wherein: the symbol: "*" indicates the point of attachment of each of the moieties of partial Formulas (5.0.0) through (5.0.10), inclusive, to $R_{\text{region } \gamma}$;

-- R^{60}_b through R^{60}_g , inclusive, R^{60}_k , and R^{60}_l are each a member selected from the group consisting of hydrogen; $-\text{CO}_2\text{R}^4$; $-\text{C}(=\text{O})\text{NR}^4_a\text{R}^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_a\text{R}^4_b$; where: R^4 ; R^4_a ; and R^4_b are as defined above but selected on an independent basis; $\rightarrow\text{O}$; $(\text{C}_1.\text{C}_2)\text{alkylcarbonyl}$; $-(\text{C}_1.\text{C}_4)\text{alkyl}$; $-(\text{CH}_2)_n(\text{C}_3.\text{C}_7)\text{cycloalkyl}$; $-(\text{C}_2.\text{C}_3)\text{alkenyl}$; $-(\text{CH}_2)_n(\text{phenyl})$; and $-(\text{CH}_2)_n(\text{HET}_1)$, where n is an integer independently selected from 0, 1, and 2; wherein said $(\text{C}_1.\text{C}_4)\text{alkyl}$, alkenyl, cycloalkyl, phenyl, and heterocyclyl groups are independently substituted with 0 to 3 substituents R^{66} , where:

-- HET_1 is a heterocyclyl group selected from the group consisting of thienyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; and morpholinyl; where:

-- R^{66} is a member selected from the group consisting of $-\text{F}$; $-\text{Cl}$; $-\text{OH}$; cyano; $-\text{C}(=\text{O})\text{OR}^{68}$; $-\text{C}(=\text{O})\text{NR}^{68}\text{R}^{69}$; $-\text{NR}^{68}\text{R}^{69}$; $-\text{NR}^{68}\text{C}(=\text{O})\text{R}^{69}$; $-\text{NR}^{68}\text{C}(=\text{O})\text{OR}^{69}$; $-\text{NR}^{68}\text{S}(=\text{O})_2\text{R}^{69}$; $-\text{S}(=\text{O})_2\text{NR}^{68}\text{R}^{69}$; $(\text{C}_1.\text{C}_4)\text{alkyl}$ including dimethyl, and $(\text{C}_1.\text{C}_4)\text{alkoxy}$ wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl ; $(\text{C}_1.\text{C}_2)\text{alkoxycarbonyl}$; $(\text{C}_1.\text{C}_2)\text{alkylcarbonyl}$; and $(\text{C}_1.\text{C}_2)\text{alkylcarbonyloxy}$, where:

---- R^{68} and R^{69} are each a member selected from the group consisting of hydrogen; and $(\text{C}_1.\text{C}_2)\text{alkyl}$; and where said:

-- R^{61}_a ; R^{61}_d ; R^{61}_e ; and R^{61}_h through R^{61}_l inclusive; R^{64}_a through R^{64}_l inclusive; R^{65}_a through R^{65}_c inclusive; and R^{65}_g through R^{65}_l inclusive are each a member selected from the group consisting of hydrogen; $-\text{OH}$; $-\text{CF}_3$; cyano; $-(\text{C}_1.\text{C}_3)\text{alkoxy}$; $-\text{C}(=\text{O})\text{OR}^4$; $-\text{C}(=\text{O})\text{NR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{OR}^4_b$; $-\text{NR}^4_a\text{S}(=\text{O})_p\text{R}^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_a\text{R}^4_b$; where: R^4 ; R^4_a ; and R^4_b are as defined further above but selected on an independent basis; $-(\text{C}_1.\text{C}_4)\text{alkyl}$; $-(\text{CH}_2)_n(\text{C}_3.\text{C}_7)\text{cycloalkyl}$; $-(\text{C}_2.\text{C}_3)\text{alkenyl}$; $-(\text{CH}_2)_n(\text{phenyl})$; and $-(\text{CH}_2)_n(\text{HET}_1)$, where n is an integer selected from 0, 1, and 2; wherein said $(\text{C}_1.\text{C}_4)\text{alkyl}$, alkenyl, cycloalkyl, phenyl, and heterocyclyl groups where heterocyclyl groups is as defined above, are independently substituted with 0 to 3 substituents R^{66} where:

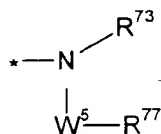
---- R^{66} is as defined above, or:

-- R^{64}_a through R^{64}_c inclusive; R^{64}_g through R^{64}_l inclusive; R^{65}_a through R^{65}_c inclusive; and R^{65}_g through R^{65}_l inclusive may be taken together in their same subscript denominated pairs along with the remaining portions of the moieties of partial Formulas (5.0.0) through (5.0.2), and (5.0.6) through (5.0.8), to form a fused bicyclic ring system comprising a member independently selected from the group consisting of benzimidazolyl; purinyl, i.e.,

imidazopyrimidinyl; and imidazopyridinyl; wherein said fused bicyclic ring system is independently substituted with 0 to 3 substituents R^{66} , where R^{66} has the same meaning as set out further above, except that it is independently selected therefrom;

5 -B. a (substituted)-amide, carbamate, or urea moiety selected from the group consisting of:

-1. alkyl-, cycloalkyl-, and alkenyl-(substituted)-amide, carbamate, or urea moieties of partial Formula (5.1.0):

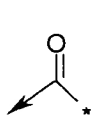


(5.1.0)

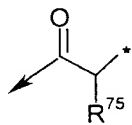
10 ---wherein: the symbol " *" is as defined above;

--- R^{73} is a member selected from the group consisting of hydrogen and $(C_1 - C_2)$ alkyl;

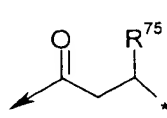
--- W^5 is selected from the group consisting the moieties of partial Formulas (5.1.1) through (5.1.12):



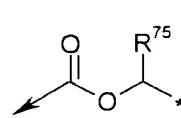
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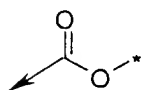
(5.1.2)



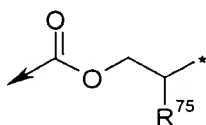
(5.1.3)



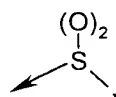
(5.1.4)



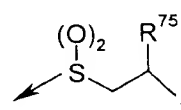
(5.1.5)



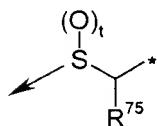
(5.1.6)



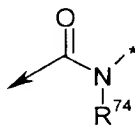
(5.1.7)



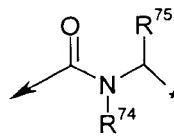
(5.1.8)



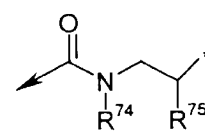
(5.1.9)



(5.1.10)



(5.1.11)



(5.1.12)

20 ----wherein: the symbol: "→" indicates the point of attachment of the moiety W^5 represented by partial Formulas (5.1.1) through (5.1.12), inclusive, to the nitrogen atom in partial Formula (5.1.0), and the symbol: " *" indicates the point of attachment of the moiety W^5 to R^{77} as defined further below;

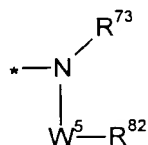
---R⁷⁴ and R⁷⁵ are each selected from the group consisting of hydrogen; (C₁-C₂)alkyl substituted by 0 or 1 substituent independently selected from OH; and (C₁-C₂)alkoxy; and

5 ---R⁷⁷ is a member selected from the group consisting of (C₁-C₆)alkyl; (C₂-C₆)alkenyl; and -(CH₂)_n-(C₃-C₇)cycloalkyl, where n is an integer selected from 0, 1, and 2; and wherein said alkyl, alkenyl, and cycloalkyl groups comprising R⁷⁷ are substituted with 0 to 3 substituents R⁷⁸, where:

---R⁷⁸ is a member selected from the group consisting of oxo; -OH; -(C₁-C₂)alkyl; -(C₁-C₃)alkoxy; -CF₃; -C(=O)OR⁷⁹; -C(=O)NR⁷⁹R⁸⁰; -NR⁷⁹R⁸⁰; -NR⁷⁹C(=O)R⁸⁰; -NR⁷⁹C(=O)OR⁸⁰; -NR⁷⁹S(=O)₂R⁸⁰; and -S(=O)₂NR⁷⁹R⁸⁰, where:

10 -----R⁷⁹ and R⁸⁰ are each a member independently selected from the group consisting of hydrogen; and (C₁-C₄)alkyl; and

-2. aryl and heterocyclyl-(substituted)-amide, carbamate, or urea moieties of partial Formula (5.2.0):



15

(5.2.0)

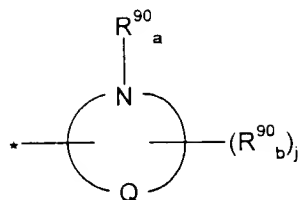
---wherein: the symbol: " * "; R⁷³; and W⁵ have the same meanings as under the definitions of partial Formula (5.1.0) above, except that they are independently selected therefrom; and under W⁵ the symbols: "→" and " * " are as defined under partial Formula (5.1.0); and

20 ---R⁸² is a member selected from the group consisting of phenyl; cinnolyl; furyl; thienyl; pyrrolyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; imidazolyl; imidazolyl; pyrazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; indolyl; isoindolyl; indolyl; benzo[b]furanyl; 2,3-dihydrobenzofuranyl; benzo[b]thiophenyl; 1H-indazolyl; benzimidazolyl; benzthiazolyl; quinolyl; isoquinolyl; phthalazinyl; quinazolyl; quinoxalyl; wherein:

25 -----the aryl or heterocyclyl moiety is substituted by 0 to 3 substituents R⁷⁸ where R⁷⁸ is as defined above, but selected on an independent basis; or

-C. a (substituted)-heterocyclyl moiety independently selected from the group consisting of:

-1. a heterocyclyl moiety of partial Formula (5.3.0):



(5.3.0)

--wherein: the symbol: "*" indicates the point of attachment of partial Formula (5.3.0) to Region Y; Q is N, O or S and

5 --partial Formula (5.3.0) represents:

---a. a monocyclic heterocyclic group containing a total of 5- members of which one said member is nitrogen and a second said member is selected from O and S where said S may optionally be in the sulfonate form, wherein said heterocyclic group is selected from the group consisting of oxazolyl; isoxazolyl; thiazolyl; and iso-thiazolyl; or

10 ----b. a monocyclic heterocyclic group containing a total of 5- members of which two said members are nitrogen and a third or fourth said member is independently selected from N, O, and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; wherein said heterocyclic group is independently selected from the group consisting of triazolyl; tetrazolyl; oxadiazolyl; and thiadiazolyl; and

15 -- R^{90}_a and R^{90}_b are each a member independently selected from the group consisting of hydrogen, $-(C_1-C_2)$ alkylcarbonyl; $-(C_1-C_4)$ alkyl; $-(CH_2)_n-(C_3-C_7)$ cycloalkyl; $-(C_2-C_3)$ alkenyl; $-(CH_2)_n$ (phenyl); and $-(CH_2)_n$ (HET₂), where n is an integer independently selected from 0, 1, and 2; wherein said (C_1-C_4) alkyl, alkenyl, cycloalkyl, phenyl, and HET₂ groups are independently substituted with 0 to 3 substituents R^{91} , where:

20 ---j has the same meaning as set forth above, but is selected on an independent basis therefrom;

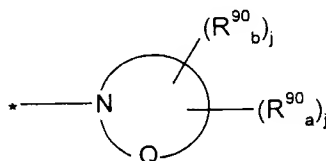
---HET₂ is a heterocyclyl group selected from the group consisting of thienyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; and morpholinyl; where:

25 ---- R^{91} is selected from the group consisting of -F; -Cl; $-CO_2R^4$; -OH; -CN; $-CONR^{93}R^{94}$; $-NR^{93}R^{94}$; $C(=O)(C_1-C_4)$ alkyl; $-NR^{93}C(=O)R^{94}$; $-NR^{93}C(=O)OR^{94}$; $-NR^{93}S(=O)R^{94}$; $-S(=O)NR^{93}R^{94}$; (C_1-C_4) alkyl including dimethyl, and (C_1-C_4) alkoxy wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; (C_1-C_2) alkoxycarbonyl; (C_1-C_2) alkylcarbonyl; and (C_1-C_2) alkylcarbonyloxy;

30 wherein:

-----R⁹³ and R⁹⁴ are each a member independently selected from the group consisting of hydrogen; and (C₁-C₂)alkyl; and

2. a heterocyclyl moiety of partial Formula (5.4.0):



(5.4.0)

---wherein: R^{90a}; R^{90b}; and j have the same meanings as set out above, but are selected independently.

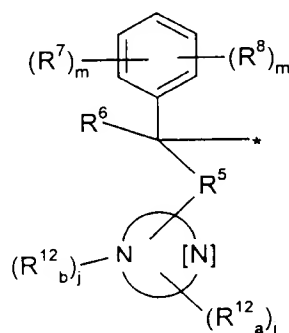
Attention is drawn to our copending application nos P60190WO and P60191WO..

10 An important aspect of the present invention is the limitation to R_{region γ}. The copending case relates to alternative limitations of Formula (I).

This invention also provides pharmaceutical formulations and dosage forms including as an active ingredient a compound of Formula I. Use of a compound of Formula I in manufacture of a formulation or dosage form and methods of treatment are also provided.

15 [R_{region α}] is at the left-hand end of the CCR5 receptor modulator of the present invention. The region designated as R_{region α} may comprise a moiety selected from several different classes of substituent components, all of which may be and are preferably isosteres of each other.

20 The first class of R_{region α} substituent components (under A.) are heterocyclyl phenylmethylene moieties as described further below. A preferred group of heterocyclyl phenylmethylene moiety embodiments (under A.1.) comprises the group consisting of hetero-phenylmethylene moieties of partial Formula (1.0.0),



(1.0.0)

The substituent R^5 is a member independently selected from the group consisting of a direct bond; $-O-$; $-C(=O)-$; $-NR^4-$; and $-S(=O)_p-$; where

R^4 is hydrogen or (C_1-C_2) alkyl.

- 5 The substituent R^6 is a member independently selected from the group consisting of hydrogen; (C_1-C_2) alkyl; (C_1-C_2) alkoxy; $-C(=O)NH_2$; $-CN$; and $-OH$. Most preferably R^6 is hydrogen and there is no substituent at this position.

Included within the partial Formula (1.0.0) are position isomer variations thereof that are not shown, but that arise where the optional substituents R^7 and R^8 are different. Substituents R^7 and R^8 are present once or twice or not at all, as indicated by their representation as: " $(R^7)_m$ " and " $(R^8)_m$ ", where m is defined as being an integer selected from 0, 1, and 2. In the most preferred embodiments of the present invention, m is 0, although in alternative embodiments m is 1.

- 15 The substituents R^7 and R^8 comprise $-F$; $-Cl$; $-CO_2R^4$; $-OH$; $-CN$; $-CONR^4_aR^4_b$; $-NR^4_aR^4_b-$; $-NR^4_aC(=O)R^4_b$; $-NR^4_aC(=O)OR^4_b$; $-NR^4_aS(=O)_pR^4_b$; $-S(=O)_pNR^4_aR^4_b$; (C_1-C_4) alkyl including dimethyl, and (C_1-C_4) alkoxy wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from $-F$ and $-Cl$; (C_1-C_2) alkoxycarbonyl; (C_1-C_2) alkylcarbonyl; and (C_1-C_2) alkylcarbonyloxy. The substituents R^4_a and R^4_b , in turn, are selected from hydrogen and (C_1-C_2) alkyl. With regard to the R^7 and R^8 substituent groups, it is preferred that they are absent ($m = 0$); or that if they are present, that they be methyl; cyclopropyl, cyclobutyl; methoxy; $-COOH$; $-OH$; $-F$; $-Cl$; $-COO(C_1-C_2)$ alkyl; or $-CF_3$. Of these choices, the more preferred substituent choices for R^7 and R^8 are that they are absent or that they are $-F$ or Cl .

- 25 R^5 as defined by Formula (1.0.0) is preferably a direct bond. The moiety R^5 may alternatively be selected from $-O-$; $-C(=O)-$; $-NR^4-$ where R^4 is hydrogen or (C_1-C_2) alkyl; and $-S(=O)_p-$.

- In partial Formula (1.0.0), the presence of substituent R^{12}_a is determined by the subscript " j ", which is an integer independently selected from 0, 1, and 2. Where j is 0, accordingly, the substituent R^{12}_a will be absent. Where j is 1 or 2, there may be one or two substituents R^{12}_a present, and these may be attached to any available carbon atom in partial Formula (1.0.0).

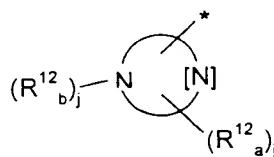
- 35 R^{12}_a is a member independently selected from the group consisting of hydrogen; $-F$; $-Cl$; $-CO_2R^4$ where R^4 is hydrogen or (C_1-C_2) alkyl as already defined above; $-oxo$; $-OH$; $-CN$; $-NH_2$; $-NH(C_1-C_2)$ alkyl; $-N(C_1-C_2)_2$ dialkyl; $-CF_3$; (C_1-C_4) alkyl; (C_2-C_4) alkenyl; (C_1-C_4) alkoxy; (C_3-C_7) cycloalkyl; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl groups

are substituted with 0 to 2 substituents R^9 wherein R^9 is a member independently selected from the group consisting of -F; -Cl; $-\text{CO}_2R^4$ where R^4 is hydrogen or $(C_1 .C_2)\text{alkyl}$; -OH; cyano; $-\text{CONR}^4_aR^4_b$; $-\text{NR}^4_aR^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})R^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{OR}^4_b$; $-\text{NR}^4_a\text{S}(=\text{O})_pR^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_aR^4_b$; $(C_1 .C_4)\text{alkyl}$ including dimethyl, and $(C_1 .C_4)\text{alkoxy}$ wherein said alkyl and alkoxy are each
 5 independently substituted with 0 to 3 substituents independently selected from F and Cl; $(C_1 .C_2)\text{alkoxycarbonyl}$; $(C_1 .C_2)\text{alkylcarbonyl}$; and $(C_1 .C_2)\text{alkylcarbonyloxy}$.

Where a R^{12}_a substituent is present and consists of an alkyl, alkenyl, alkoxy, cycloalkyl or phenyl group, it may optionally be mono- or di-substituted in turn by a further substituent R^9 , which is independently selected from the above-recited groups. This includes in particular
 10 $(C_1 .C_4)\text{alkyl}$ substituted with 1 to 3 substituents independently selected from F and Cl. Accordingly, the substituent $-\text{CF}_3$ is a preferred definition of R^9 in the compounds of partial Formula (1.0.0).

The R^{12}_b substituent is attached directly to the nitrogen atom of the heterocyclic group depicted in partial Formula (1.0.0), and its presence is determined by the subscript "j", which is
 15 an integer independently selected from 0, 1, and 2. Where j is 0, accordingly, the substituent R^{12}_b is absent. In that case that the nitrogen atom is attached by a covalent double bond to an adjacent atom in the heterocyclic group depicted in partial Formula (1.0.0). Where j is 1 or 2, there will be one or two substituents R^{12}_b attached to the nitrogen atom of the heterocyclic group depicted in partial Formula (1.0.0). Where two such R^{12}_b substituents are attached, the
 20 nitrogen atom is in quaternary form. The substituent R^{12}_b is independently selected from the group consisting of hydrogen; $(C_1 .C_4)\text{alkyl}$; $(C_2 .C_4)\text{alkenyl}$; $(C_1 .C_2)\text{alkoxy}$; $(C_3 .C_7)\text{cycloalkyl}$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^9 wherein R^9 has the same meaning as in R^9 defined above, except that it is selected independently therefrom.

25 The group represented by partial Formula (1.0.1):

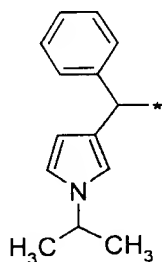


(1.0.1)

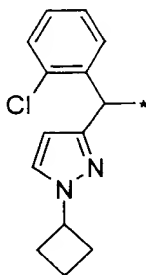
represents a monocyclic heterocyclic group, or a bicyclic benzo-fused ring system containing said heterocyclic group wherein said heterocyclic group contains a total of 5- or 6- members of
 30 which one or two of said members is nitrogen, the presence of the optional second nitrogen atom being represented by: "[N]"; wherein said heterocyclic group or ring system is selected from the group consisting of pyrrolyl; pyrazolyl; imidazolyl; pyridinyl; pyrazinyl; pyrimidinyl;

pyridazinyl; piperazinyl; indolyl; indazolyl; benzimidazolyl; quinolyl; *iso*-quinolyl; and quinazolyl.

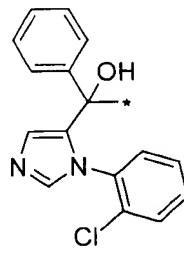
N-containing heterocyclic moieties of partial Formula (1.0.0) result in some of the following preferred embodiments of $R_{\text{region } \alpha}$, represented by partial Formulas (1.0.4) through 5 (1.0.10), inclusive:



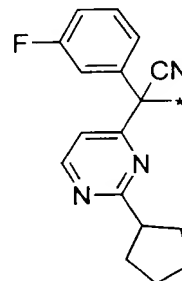
(1.0.4)



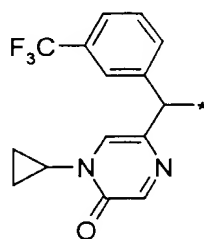
(1.0.5)



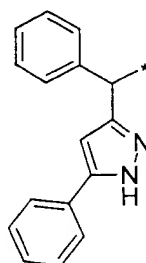
(1.0.6)



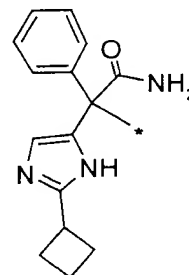
(1.0.7)



(1.0.8)

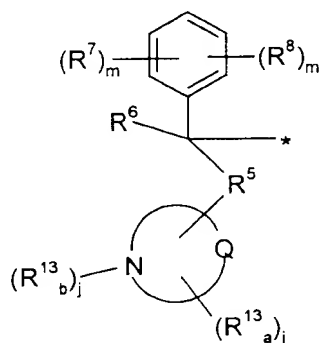


(1.0.9)



(1.0.10)

10 A further group of N-containing heterocyclic phenylmethylene moieties (under A.2 comprises several subgeneric groups within partial Formula (1.1.0):

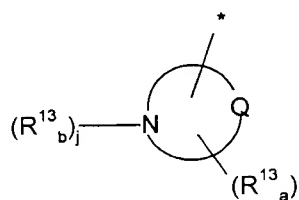


(1.1.0)

where the symbol "*" and R^5 ; R^6 ; R^7 ; R^8 ; j and m are as defined above;

and R^{13}_a is a member selected from the group consisting of hydrogen; F; Cl; $-\text{CO}_2R^4$; oxo; $-\text{OH}$; CN; NH_2 ; $\text{NH}(\text{C}_1\text{--C}_2)\text{alkyl}$; $\text{N}(\text{C}_1\text{--C}_2)_2\text{dialkyl}$; $-\text{CF}_3$; $(\text{C}_1\text{--C}_4)\text{alkyl}$; $(\text{C}_2\text{--C}_4)\text{alkenyl}$; $(\text{C}_1\text{--C}_2)\text{alkoxy}$; $(\text{C}_3\text{--C}_7)\text{cycloalkyl}$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^{11} wherein R^{11} is a member independently selected from the group consisting of F; Cl; $-\text{CO}_2R^4$; $-\text{OH}$; $-\text{CN}$; $-\text{CONR}^4_aR^4_b$; $-\text{NR}^4_aR^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})R^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{OR}^4_b$; $-\text{NR}^4_a\text{S}(=\text{O})_pR^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_aR^4_b$; $(\text{C}_1\text{--C}_4)\text{alkyl}$ including dimethyl, and $(\text{C}_1\text{--C}_4)\text{alkoxy}$ wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; $(\text{C}_1\text{--C}_2)\text{alkoxycarbonyl}$; $(\text{C}_1\text{--C}_2)\text{alkylcarbonyl}$; and $(\text{C}_1\text{--C}_2)\text{alkylcarbonyloxy}$; and R^{13}_b is selected from the group consisting of hydrogen; $(\text{C}_1\text{--C}_4)\text{alkyl}$; $(\text{C}_2\text{--C}_4)\text{alkenyl}$; $(\text{C}_1\text{--C}_2)\text{alkoxy}$; $(\text{C}_3\text{--C}_7)\text{cycloalkyl}$; $\text{C}(=\text{O})(\text{C}_1\text{--C}_4)\text{alkyl}$; $\text{S}(=\text{O})_2(\text{C}_1\text{--C}_4)\text{alkyl}$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^{11} wherein R^{11} has the same meaning as in above, except that it is independently selected therefrom.

The moiety of partial Formula (1.1.1):

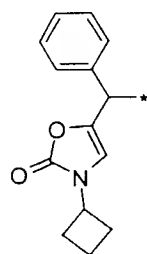


(1.1.1)

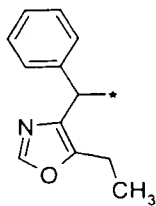
represents, *inter alia*, a monocyclic heterocyclic group containing a total of 5-members of which one said member is nitrogen and Q is selected from O and S

The heterocyclic group may be selected from the group consisting of oxazolyl; oxazolidinyl; isoxazolyl; thiazolyl; thiazolidinyl; iso-thiazolyl; morpholinyl and thiamorpholinyl.

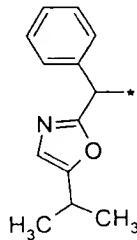
Moieties of partial Formula (1.1.0) containing the group of partial Formula (1.1.1) result in the following preferred embodiments of $R_{\text{region } \alpha}$, represented by partial Formulas (1.1.3) through (1.1.9):



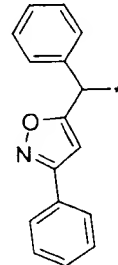
(1.1.3)



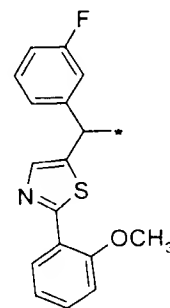
(1.1.4)



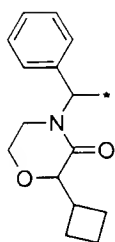
(1.1.5)



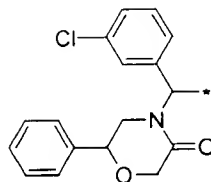
(1.1.6)



(1.1.7)



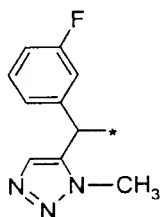
(1.1.8)



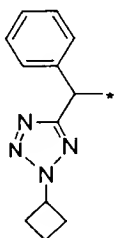
(1.1.9)

In alternative preferred embodiments the heterocyclic group may be selected from the group consisting of triazolyl; triazinyl; tetrazolyl; oxadiazolyl; and thiadiazolyl.

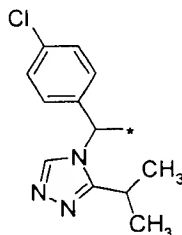
- 5 Further preferred embodiments of $R_{\text{region } \alpha}$, are represented by partial Formulas (1.1.20) through (1.1.24), inclusive:



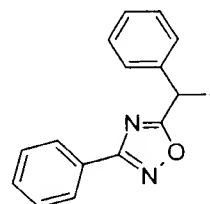
(1.1.20)



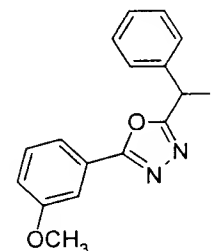
(1.1.21)



(1.1.22)



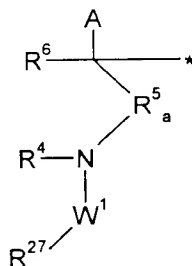
(1.1.23)



(1.1.24)

- 10 Another class of which $R_{\text{region } \alpha}$ moieties (under B) are (substituted)-amido-aryl or -heterocyclyl moieties which may be independently selected from several groups, as described in more detail below.

The first such class of (substituted)-amido-aryl or -heterocyclyl moieties of $R_{\text{region } \alpha}$ are those in which the amido-aryl or -heterocyclyl portion of the group is substituted by alkyl-, alkenyl-, or alkynyl, as represented by partial Formula (2.0.0)

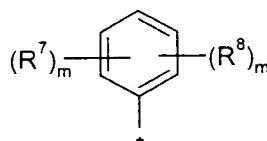


(2.0.0)

15

where the symbol "*" and R^4 and R^6 ; and m, R^7 and R^8 in the further definition of A; are as defined in the partial formulas above, except that all of the above-recited substituents are selected independently.

The moiety A in partial Formula (2.0.0) is a member independently selected from the group consisting of several different classes of moieties, as discussed below. The first class represented by partial Formula (2.0.3) is a preferred embodiment of this invention



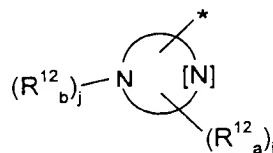
5

(2.0.3)

wherein the symbols R^7 ; R^8 and m are as defined in the partial formulas further above, except that all of the above-recited substituents are selected independently of their selection in said partial formulas further above; and the symbol: "*" indicates the point of attachment of the moiety A to the other, remaining portions of partial Formula (2.0.0).

10

Further embodiments of moiety A are depicted by partial Formulas (2.0.4) and (2.0.5). Partial Formula (2.0.4) is:

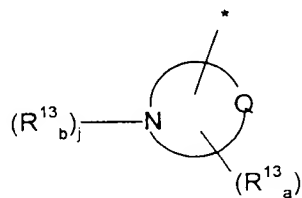


(2.0.4)

which represents a monocyclic heterocyclic group, selected from the group consisting of pyrrolyl; pyrazolyl; imidazolyl; pyridinyl; pyrazinyl; and pyrimidinyl. It is noted that in the moiety of partial Formula (2.0.3), the symbols R^{12}_a and R^{12}_b , and the subscript "j" which determines their presence, are as defined in the partial formulas further above, except that "j" is 0 or 1 and all of the above-recited substituents are selected independently of their selection further above; and the symbol: "*" indicates the point of attachment of the moiety A to the other, remaining portions of partial Formula (2.0.0).

20

Further embodiments of moiety A are depicted by partial Formula (2.0.5)



(2.0.5)

which represents a monocyclic heteroaromatic group containing a total of 5- members of which one said member is nitrogen and Q is selected from O and S where said S may optionally be in the sulfonate form, $-S(=O)_2$. Said heterocyclic group may be selected from the group consisting of oxazolyl; isoxazolyl; thiazolyl; and *iso*-thiazolyl; triazolyl; triazinyl; tetrazolyl; oxadiazolyl; and thiadiazolyl. It is noted that the symbols R^{13}_a and R^{13}_b , and the subscript "j" which determines their presence, are as defined in the partial formulas further above, except that "j" is 0 or 1 and all of the above-recited substituents are selected independently of their selection in said partial formulas further above; and the symbol: "*" indicates the point of attachment of the moiety A to the other, remaining portions of partial Formula (2.0.0).

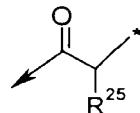
The group R^5_a is selected from a direct bond; $-C(=O)-$; and $-S(=O)_2-$. In preferred embodiments of the present invention R^5_a is a direct bond. It is provided, however, that where R^5_a is $-CO-$ or $-SO_2-$, the divalent moiety W^1 is defined to additionally include the meaning of being a direct bond.

In partial Formula (2.0.0), R^{27} is a member selected from the group consisting of (C_1-C_6) alkyl; (C_2-C_6) alkenyl; and (C_2-C_6) alkynyl; wherein said alkyl, alkenyl, and alkynyl groups comprising R^{27} may be substituted with 0 to 3 substituents R^{28} where R^{28} is selected from the group consisting of F; Cl; oxo; hydroxy; (C_1-C_2) alkyl; (C_1-C_3) alkoxy; $-C(=O)OR^{29}$; $C(=O)(C_1-C_4)$ alkyl; $-S(=O)_2(C_1-C_4)$ alkyl; $-C(=O)NR^{29}R^{30}$; $-NR^{29}R^{30}$; $-NR^{29}C(=O)R^{30}$; $-NR^{29}C(=O)OR^{30}$; $-NR^{29}S(=O)_2R^{30}$; and $-S(=O)_2NR^{29}R^{30}$, where R^{29} and R^{30} are independently selected from hydrogen and (C_1-C_4) alkyl.

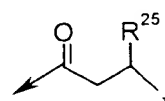
The moiety W^1 is a member independently selected from the group consisting of divalent moieties of partial Formulas (2.0.6) through (2.0.16), inclusive:



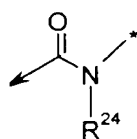
(2.0.6)



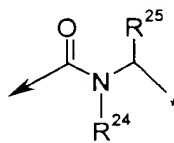
(2.0.7)



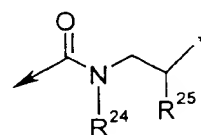
(2.0.8)



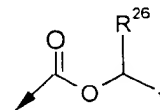
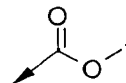
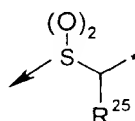
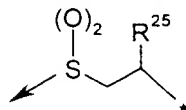
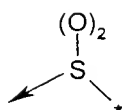
(2.0.19)



(2.0.10)



(2.0.11)



(2.0.12)

(2.0.13)

(2.0.14)

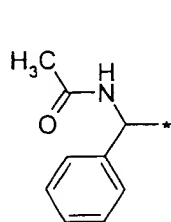
(2.0.15)

(2.0.16)

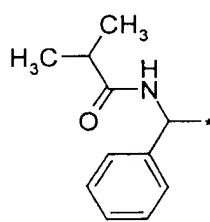
where the symbol: " \rightarrow " indicates the point of attachment of the moiety W^1 to the
 5 nitrogen atom in partial Formula (2.0.0), and the symbol: "*" indicates the point of attachment
 of the moiety W^1 to the moiety R^{27} which represents the remaining portions of partial Formula
 (2.0.0); and R^{25} and R^{26} are each independently a member selected from the group consisting
 of hydrogen; (C_1-C_2) alkyl substituted by 0 or 1 substituent independently selected from F and
 OH; and (C_1-C_2) alkoxy.

10 The bridging element $-N(R^4)-W^1-$ may alternatively constitute or contain several
 different functionalities. The first and most preferred of these is an amide functionality, which
 may be represented as: $-NR^4-C(=O)-$. Other functionality types include sulfonamido and
 ureido moieties within the scope of partial Formulas (2.0.6) through (2.0.16).

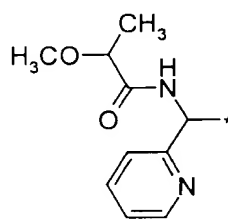
Preferred alkyl and alkenyl groups R^{27} include: methyl; ethyl; *iso*-propyl; *t*-butyl; and
 15 propenyl (allyl). These alkyl and alkenyl groups may be substituted by 0 to 3 substituents R^{28} .
 It is preferred that where a substituent is present that it be a single substituent independently
 selected from F; Cl; OH; CF_3 ; CH_3 ; OCH_3 ; CN; NH_2 ; $NHCH_3$; $N(CH_3)_2$; $NHCOCH_3$ and
 $NCH_3(COCH_3)$. Consequently, groups of partial Formula (2.0.0) which are preferred
 embodiments of the present invention constituting $R_{\text{region } \alpha}$ include the following moieties of
 20 partial Formulas (2.0.30) through (2.0.36), inclusive:



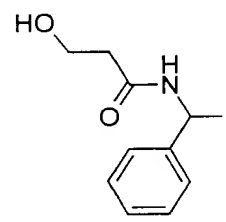
(2.0.30)



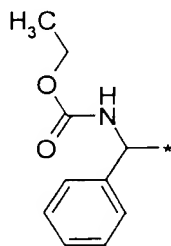
(2.0.31)



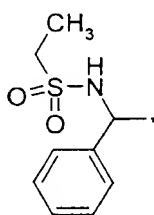
(2.0.32)



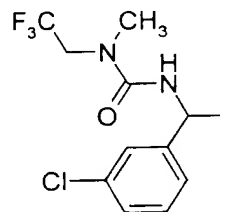
(2.0.33)



(2.0.34)

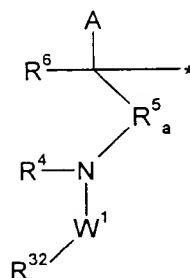


(2.0.35)



(2.0.36)

The second class of (substituted)-amido-aryl moieties comprising $R_{\text{region } \alpha}$ are those in which the amido-aryl portion of the group is substituted by -(cycloalkyl) or -alkyl(cycloalkyl), as represented by partial Formula (2.1.0).

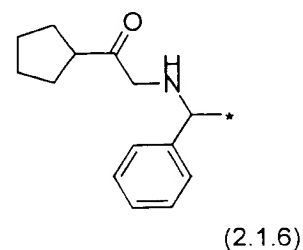
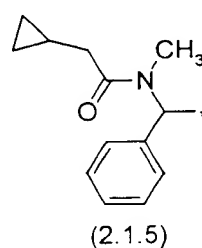
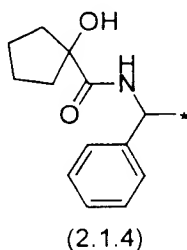
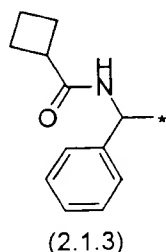


(2.1.0)

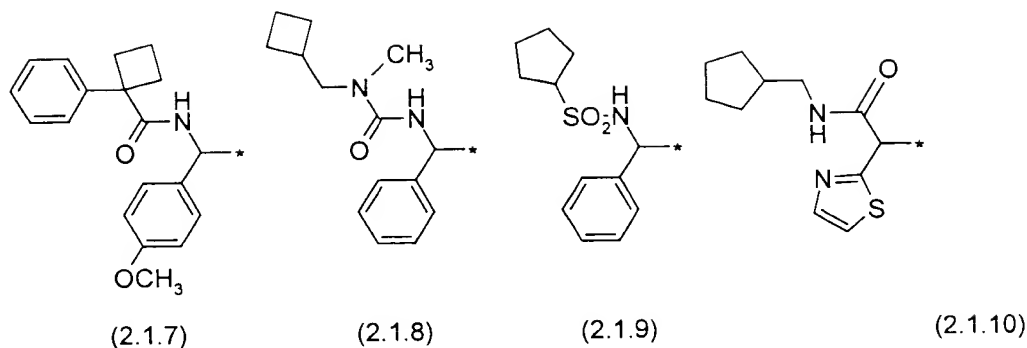
5

where; A; W^1 ; the symbol "*" and R^4 ; R^5_a ; R^6 ; and m, R^7 and R^8 in the further definition of A; have the same meaning as set out in the partial formulas further above, except that all of the above-recited substituents are selected independently of their selection further above. R^{32} is a member independently selected from the group consisting of -
 10 $-(CH_2)_n-(C_3-C_7)\text{cycloalkyl}$, where n is an integer selected from 0, 1, and 2; in the event n is 0, then the α -carbon atom of said $(C_3-C_7)\text{cycloalkyl}$ may be substituted by $(C_1-C_4)\text{alkyl}$ or phenyl, where said alkyl or phenyl may be substituted by 1, or 2 of CH_3 , OCH_3 , OH or NH_2 ; and in the event that n is 1 or 2, the resulting methylene or ethylene group may be substituted by F; Cl; CN; NH_2 ; $N(CH_3)_2$; OH ; OCH_3 ; $(C_1-C_4)\text{alkyl}$; or phenyl. It will also be further noted that the
 15 basic $(C_3-C_7)\text{cycloalkyl}$ group comprising R^{32} may also be substituted by 0 to 3 substituents R^{28} where R^{28} has the same meaning as defined further above with respect to substituents for group R^{27} under partial Formula (2.0.0), but independently selected therefrom.

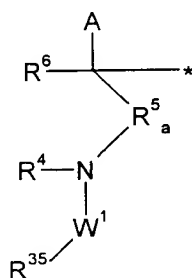
Representative cycloalkyl and alkylcycloalkyl groups within the scope of R^{32} include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; cyclopropylmethyl; cyclobutylethyl;
 20 cyclopentylpropmethyl; and cyclopentylmethyl. More preferred single substituents for these cycloalkyl and alkylcycloalkyl groups include F, Cl, and CN, especially OH ; OCH_3 ; and NH_2 . Accordingly, groups of partial Formula (2.1.0) which are preferred embodiments of $R_{\text{region } \alpha}$ include partial Formulas (2.1.3) through (2.1.10).



25



The third class of (substituted)-amido-aryl moieties of $R_{\text{region } \alpha}$ are those in which the amido-aryl portion of the group is substituted by aryl- and heterocyclyl-substituted-amido-aryl moieties of partial Formula (2.2.0).



(2.2.0)

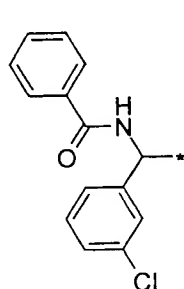
where A; W^1 ; the symbol " * " and R^4 ; R^5_a ; R^6 ; and m, R^7 and R^8 in the definition of A; have the same meaning as set out above, except that all of the above-recited substituents are selected independently.

The moiety R^{35} may be selected from the group consisting of phenyl; furyl; tetrahydropyranyl; tetrahydrofuranyl; oxetanyl; thienyl; pyrrolyl; pyrrolidinyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; imidazolyl; imidazolynyl; pyrazolyl; pyrazolynyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; piperazinyl; pyrimidinyl; pyranyl; azetidynyl; morpholynyl; parathiazinyl; indolyl; isoindolyl; 3H-indolyl; indolynyl; benzo[b]furanyl; 2;3-dihydrobenzofuranyl; benzothienyl; 1H-indazolyl; benzimidazolyl; benzoxazolyl; benzisoxazolyl; benzthiazolyl; benzoxdiazolyl; quinolynyl; isoquinolynyl; phthalazinyl; quinazolinyl; and quinoxalynyl.

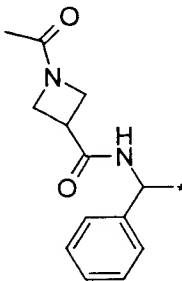
Preferred meanings of R^{35} are phenyl; pyrrolyl; oxazolyl; imidazolyl; pyridinyl; pyrimidinyl; triazolyl; indolyl; benzimidazolyl; benzotriazolyl; quinolynyl; thienyl; furfuryl; benzofuranyl; thiazolyl; oxazolyl; isoxazolyl; oxadiazolyl; and benzoxazolyl; and benzoxadiazolyl. Most preferred are tetrahydropyranyl; oxetanyl; azetidynyl and tetrahydrofuranyl. Group R^{35} may be substituted by 3 substituents R^{28} where R^{28} has the same meaning as defined above but selected independently.

Alternative aryl and heterocyclyl groups falling within the scope of R^{35} include phenyl; pyrrolyl; imidazolyl; pyridyl; oxazolyl; furyl; and benzofuranyl. Preferred single or double substituents for these groups include -CN; -F; -Cl; -CONH₂; -CH₃; -CF₃; and -OCH₃.

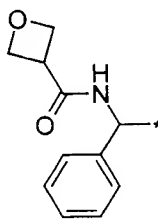
Accordingly, groups of partial Formula (2.2.0) which are preferred embodiments of $R_{\text{Region } \alpha}$ include partial Formulas (2.2.3) through (2.2.14)



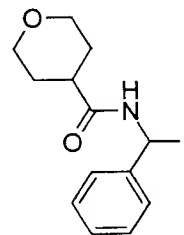
(2.2.3)



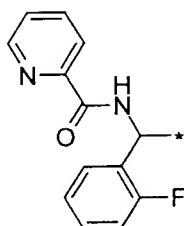
(2.2.4)



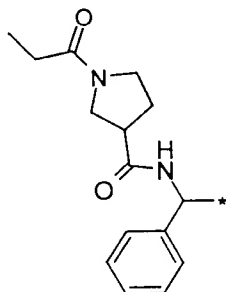
(2.2.5)



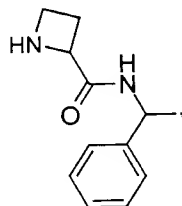
(2.2.6)



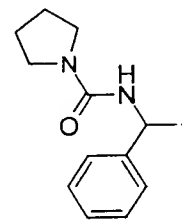
(2.2.7)



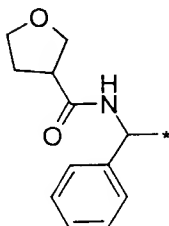
(2.2.8)



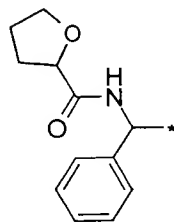
(2.2.9)



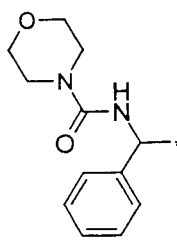
(2.2.10)



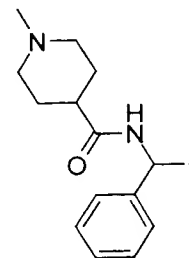
(2.2.11)



(2.2.12)



(2.2.13)



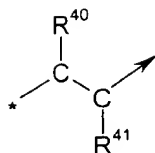
(2.2.14)

10

$[R_{\text{Region } \beta}]$ may be considered to be to the left-hand end of the molecule of the present invention as depicted, and comprises a bridging element between $R_{\text{Region } \alpha}$ described above, and $R_{\text{Region } \gamma}$ described below.

15

The alkyl bridging element of $R_{\text{Region } \beta}$ comprises a moiety of partial Formula (3.0.0):

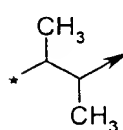


(3.0.0)

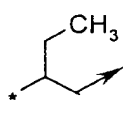
- where the symbol " * " represents the point of attachment of the alkyl bridging element moiety of partial Formula (3.0.0) to $R_{\text{region } \alpha}$ of the modulator compound of Formula (I); and the
- 5 symbol "→" represents the point of attachment of the alkyl bridging element moiety of partial Formula (3.0.0) to $R_{\text{region } \gamma}$ of the modulator compound of Formula (I). Substituents R^{40} and R^{41} are both independently selected from the group consisting of hydrogen; (C₁-C₂) alkyl including dimethyl; hydroxy; and (C₁-C₃) alkoxy; provided that only one of R^{40} and R^{41} may be (C₁-C₃) alkoxy or hydroxy, the other one of R^{40} or R^{41} being selected from hydrogen and
- 10 (C₁-C₂) alkyl including dimethyl.

Accordingly, R^{40} and R^{41} may be hydrogen; methyl; ethyl; dimethyl, *i.e.*, two methyl groups joined to the single carbon atom to which R^{40} or R^{41} is attached; hydroxy; methoxy; ethoxy; or propoxy.

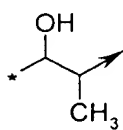
- Some representative embodiments of the alkyl bridging element of partial Formula
- 15 (3.0.0) include the following moieties of partial Formulas (3.0.1) through (3.0.7), inclusive:



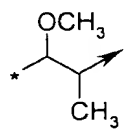
(3.0.1)



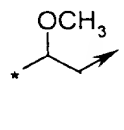
(3.0.2)



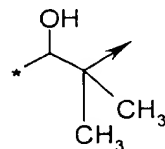
(3.0.3)



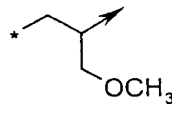
(3.0.4)



(3.0.5)

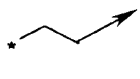


(3.0.6)

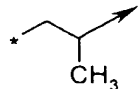


(3.0.7)

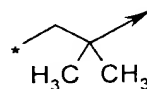
- In the most preferred embodiments of the modulator compounds of the present
- 20 invention, both R^{40} and R^{41} are hydrogen, and the alkyl bridging element of partial Formula (3.0.0) is unsubstituted ethylene. In preferred embodiments a single methyl, hydroxy, or methoxy substituent may be present, resulting in alkyl bridging elements such as those of partial Formulas (3.0.8) through (3.0.10):



(3.0.8)



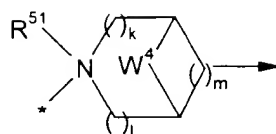
(3.0.9)



(3.0.10)

25

[$R_{\text{region } \gamma}$] comprises an aza-bicyclic moiety of partial Formula (4.2.0):



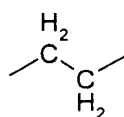
(4.2.0)

where "*" is a symbol which represents the point of attachment of the moiety of partial Formula (4.2.0) to $R_{\text{region } \beta}$ of the compound of Formula (I); and " \rightarrow " is a symbol representing the point of attachment to $R_{\text{region } \delta}$. The substituent group R^{51} is absent or is a member selected from the group consisting of: $(C_1 . C_4)$ alkyl substituted by 0 or 1 substituent independently selected from $(C_1 . C_2)$ alkoxy and $-CO_2R^4$ where R^4 is as defined above; and $\rightarrow O$; it being understood that in the case where the substituent R^{51} is present the nitrogen atom of partial Formula (4.2.0) is in quaternary form.

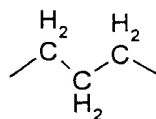
- 10 W^4 in the moiety of partial Formula (4.2.0) defines a bridging element and may be a direct bond, or selected from the group consisting of the moieties of partial Formulas (4.2.1) through (4.2.6):



(4.2.1)

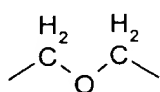


(4.2.2)

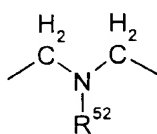


(4.2.3)

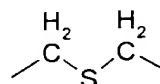
15



(4.2.4)



(4.2.5)



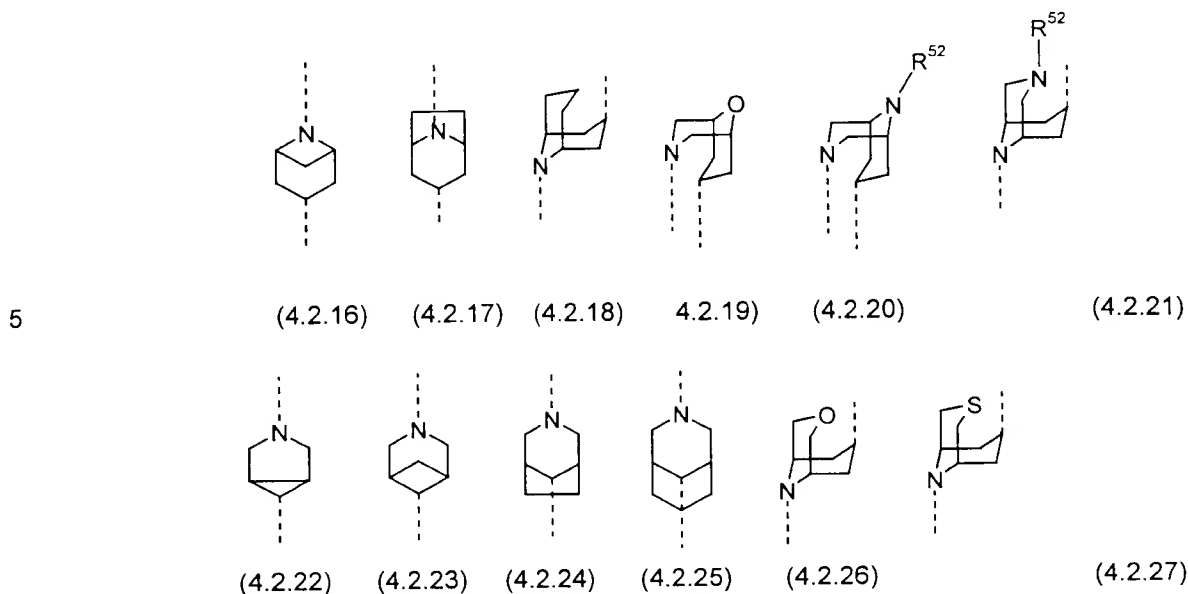
(4.2.6)

- 20 R^{52} may be selected from hydrogen phenyl; $(C_1 . C_4)$ alkyl substituted by 0 or 1 substituent independently selected from $(C_1 . C_2)$ alkoxy and $-CO_2R^4$ where R^4 is as defined further above; $(C_3 . C_6)$ cycloalkyl; $-CO_2R^4$; $(C_1 - C_2)$ alkoxycarbonyl; $\rightarrow O$; $-C(=O)NR^4_aR^4_b$; $-S(=O)_p(C_1 - C_4)$ alkyl; and $(C_1 . C_2)$ alkylcarbonyl.

The subscripts "k", "l" and "m" are each an integer independently selected from 0, 1, 2, and 3,

- 25 In preferred embodiments of partial Formula (4.2.0), there are two carbon atoms between the point of attachment to $R_{\text{region } \delta}$ and the nitrogen atom point of attachment of the moiety of partial Formula (4.2.0) to $R_{\text{region } \beta}$. Preferably, this relationship is maintained, whatever the definitions of k, l, and m.

Included among preferred embodiments of partial Formula (4.2.0) are partial Formulas (4.2.16) through (4.2.27). The dashed lines indicate the points of attachment. A number of conformers of partial Formula (4.2.0) are illustrated:

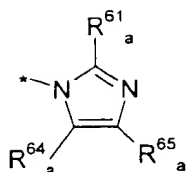


The group R^{52} is selected from hydrogen; phenyl; (C_1-C_4) alkyl substituted by 0 or 1
 10 substituent independently selected from (C_1-C_2) alkoxy and $-CO_2R^4$; (C_3-C_6) cycloalkyl;
 $C(=O)(C_1-C_4)$ alkyl; $S(=O)_2(C_1-C_4)$ alkyl; $\rightarrow O$; $-C(=O)NR^4_aR^4_b$; $-S(=O)_p(C_1-C_4)$ alkyl; and
 (C_1-C_2) alkylcarbonyl; where R^4 , R^4_a , and R^4_b are as defined further above, but selected on an
 independent basis. It is generally more preferred that the nitrogen atom be unsubstituted, *i.e.*,
 15 that R^{52} is hydrogen, but other preferred embodiments include those where R^{52} is methyl,
 methyl carboxylate, methylcarbonyl, or $\rightarrow O$. Quaternary salts also may be provided.

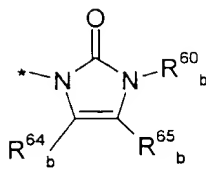
The substituent group R^{51} is preferably absent.

[$R_{\text{region } \delta}$] constitutes the right-hand end of the compounds of Formula (I) and is
 attached directly to $R_{\text{region } \gamma}$ described above. $R_{\text{region } \delta}$ comprises three different groups: bicyclic
 heterocycles; substituted amides and monocyclic heterocycles, all of which are described in
 20 detail below.

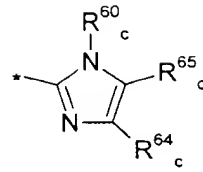
The first group of moieties (under A.) comprises two-nitrogen-atom-containing five
 membered heterocyclic moieties of partial Formulas (5.0.0) through (5.0.10):



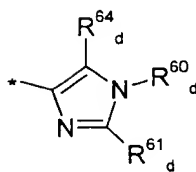
(5.0.0)



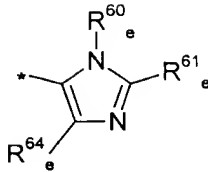
(5.0.1)



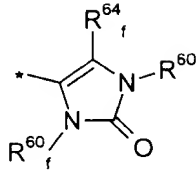
(5.0.2)



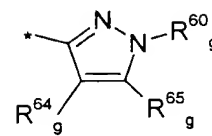
(5.0.3)



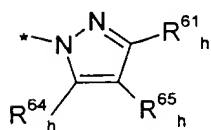
(5.0.4)



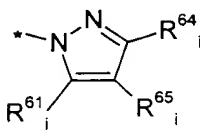
(5.0.5)



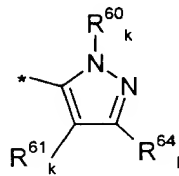
(5.0.6)



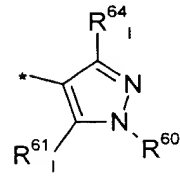
(5.0.7)



(5.0.8)



(5.0.9)



(5.0.10)

where the symbol: "*" indicates the point of attachment of each of the moieties of partial Formulas (5.0.0) through (5.0.10), inclusive, to R_{region Y}.

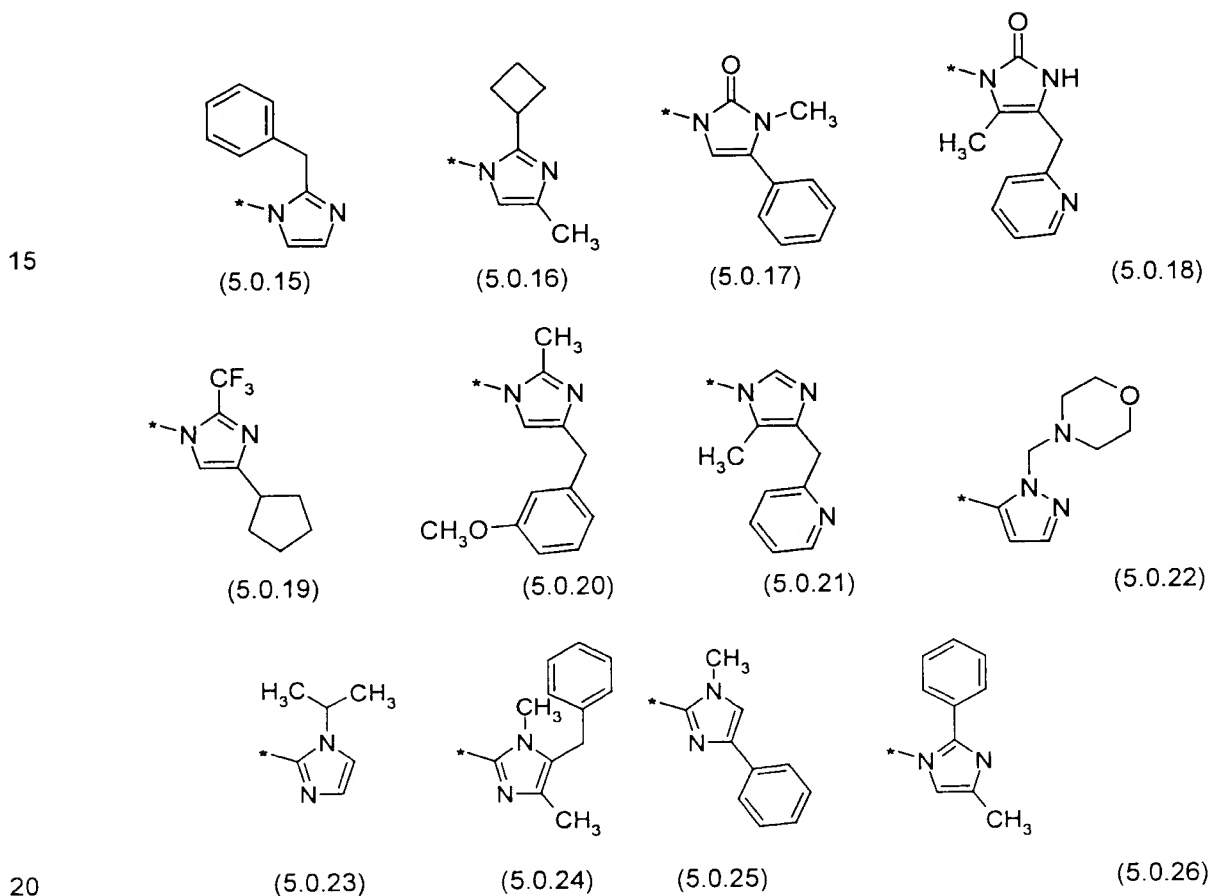
One of the two nitrogen atoms in the heterocyclic moieties of partial Formulas (5.0.0) through (5.0.10) is substituted by R⁶⁰_b through R⁶⁰_g, R⁶⁰_k, and R⁶⁰_i, and these substituents are selected from hydrogen; -CO₂R⁴; -C(=O)NR⁴_aR⁴_b; -S(=O)_pNR⁴_aR⁴_b; where: R⁴; R⁴_a; and R⁴_b are as defined further above but selected on an independent basis; →O; (C₁-C₂)alkylcarbonyl; -(C₁-C₄)alkyl; -(CH₂)_n-(C₃-C₇)cycloalkyl; -(C₂-C₃)alkenyl; -(CH₂)_n-(phenyl); and -(CH₂)_n-(HET₁), where n is an integer selected from 0, 1, and 2; wherein said (C₁-C₄)alkyl, alkenyl, cycloalkyl, phenyl, and HET₁ groups are independently substituted with 0 to 3 substituents R⁶⁶.

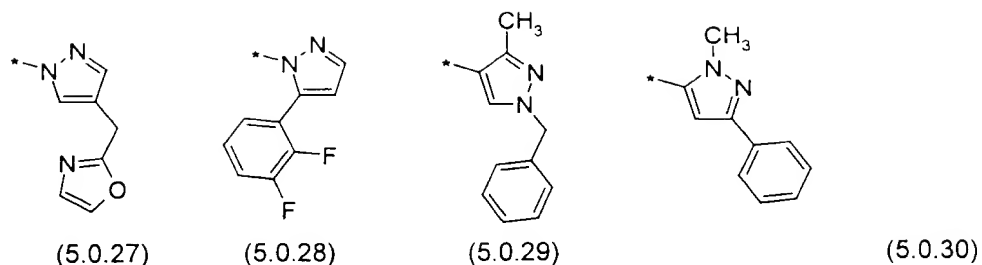
The symbol "HET₁" is intended to mean a heterocyclyl group selected from the group consisting of thienyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; and morpholinyl. The heterocyclyl group HET₁ may be attached directly or through an alkylene bridge, which is encompassed within the scope of "-(CH₂)_n-", where n is an integer selected from 0, 1, and 2. Where this heterocyclyl group, or an alkyl, alkenyl, cycloalkyl or phenyl group defining one of the R⁶⁰ groups is present, it may be substituted in turn by a substituent group R⁶⁶. The group R⁶⁶ is selected from the group consisting of -F; -Cl; -OH; -CN; -C(=O)OR⁶⁸; -C(=O)NR⁶⁸R⁶⁹; -NR⁶⁸R⁶⁹; -NR⁶⁸C(=O)R⁶⁹; -NR⁶⁸C(=O)OR⁶⁹; -NR⁶⁸S(=O)₂R⁶⁹; -S(=O)₂NR⁶⁸R⁶⁹; (C₁-C₄)alkyl including dimethyl, and (C₁-C₄)alkoxy wherein said alkyl and alkoxy are each independently

substituted with 3 substituents independently selected from F and Cl; (C₁-C₂)alkoxycarbonyl; (C₁-C₂)alkylcarbonyl; and (C₁-C₂)alkylcarbonyloxy. The substituents R⁶⁸ and R⁶⁹ are in turn selected from hydrogen and (C₁-C₂)alkyl. In the most preferred compounds of Formula (I), these nitrogen atoms will be substituted either with hydrogen or methyl.

- 5 The remaining substituents: R⁶¹_a; R⁶¹_d; R⁶¹_e; R⁶¹_h through R⁶¹_i, R⁶⁴_a through R⁶⁴_i, R⁶⁵_a through R⁶⁵_c, and R⁶⁵_g through R⁶⁵_i, are each independently selected from the group consisting of hydrogen; OH; CF₃; -CN (C₁-C₃)alkoxy; -C(=O)OR⁴; -C(=O)NR⁴_aR⁴_b; -NR⁴_aR⁴_b; -NR⁴_aC(=O)R⁴_b; -NR⁴_aC(=O)OR⁴_b; -NR⁴_aS(=O)_pR⁴_b; and -S(=O)_pNR⁴_aR⁴_b where R⁴, R⁴_a, and R⁴_b are as defined further above; -(C₁-C₄)alkyl; -(CH₂)_n-(C₃-C₇)cycloalkyl; -(C₂-C₃)alkenyl; 10 -(CH₂)_n-(phenyl); and -(CH₂)_n-(HET₁), where n is an integer selected from 0, 1, and 2 and HET₁, including possible substituents are as defined above.

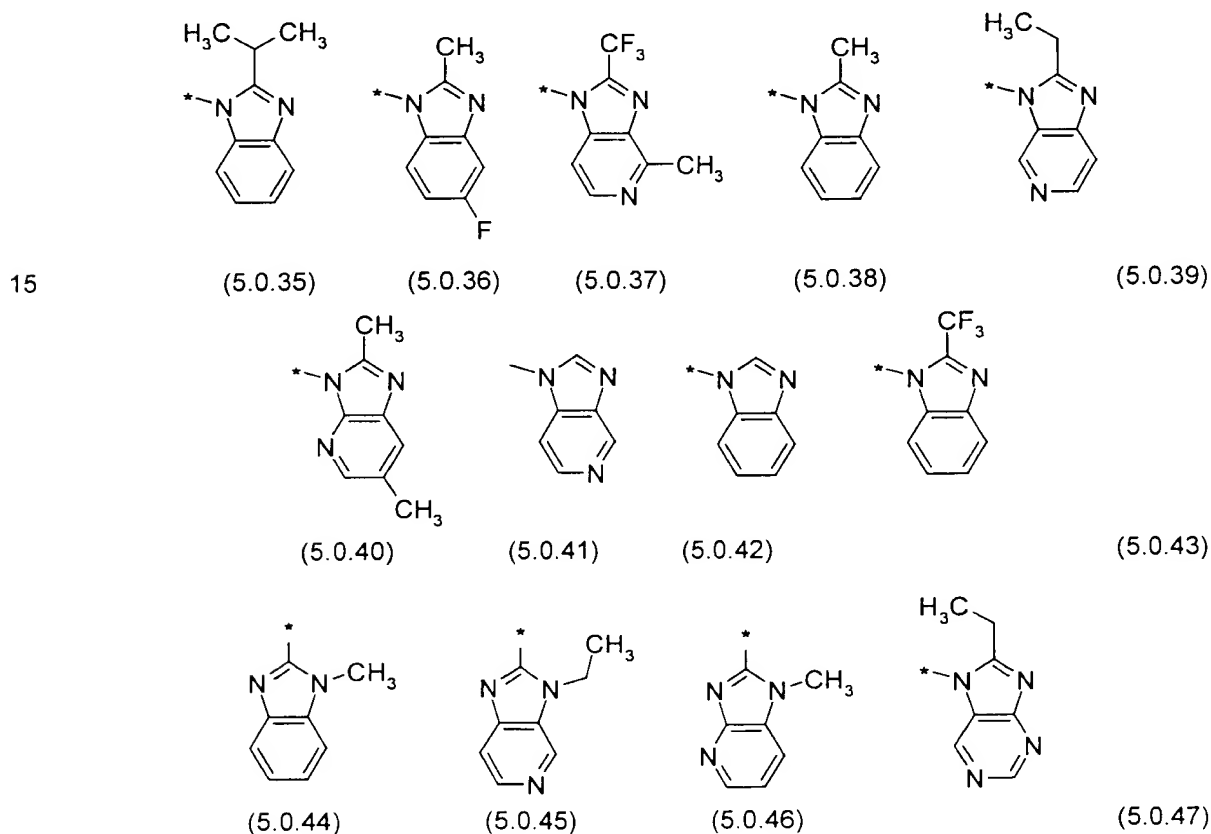
Accordingly, preferred embodiments of monocyclic heterocyclic moieties of partial Formulas (5.0.0) through (5.0.10) optionally substituted as above-described include partial Formulas (5.0.15) through (5.0.30):





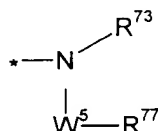
The preferred subclass of moieties under partial Formulas (5.0.0) through (5.0.10) are those wherein R^{64}_a through R^{64}_c , R^{64}_g through R^{64}_i , R^{65}_a through R^{65}_c , and R^{65}_g through R^{65}_i are taken together in their same subscript denominated pairs along with the remaining portions of the moieties of partial Formulas (5.0.0) through (5.0.10) to form a fused bicyclic ring system comprising benzimidazolyl; purinyl, *i.e.*, imidazopyrimidinyl; or imidazopyridinyl. The above-mentioned fused bicyclic ring systems are also optionally substituted with up to 3 substituents R^{66} selected from F; Cl; oxo; -OH; -CN; $(C_1-C_2)alkyl$; -CF₃; -C(=O)OR⁶⁸; -C(=O)NR⁶⁸R⁶⁹; -NR⁶⁸R⁶⁹; -NR⁶⁸C(=O)R⁶⁹; -NR⁶⁸C(=O)OR⁶⁹; -NR⁶⁸S(=O)₂R⁶⁹; and -S(=O)₂NR⁶⁸R⁶⁹, where R^{68} and R^{69} are each selected from hydrogen and $(C_1-C_2)alkyl$.

Preferred embodiments of this type of moiety under partial Formulas (5.0.0) through (5.0.10) are illustrated in the following partial Formulas (5.0.35) through (5.0.47)



Another class of moieties (under B.) defining $R_{\text{region } \delta}$ of the compounds of Formula (I) are (substituted)-amides, carbamates or ureas which includes subclasses consisting of alkyl-, cycloalkyl-, and alkenyl substituents; and aryl and heterocyclyl substituents. The first subclass

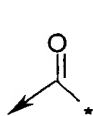
5 comprises moieties of partial Formula (5.1.0):



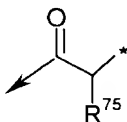
(5.1.0)

where the symbol "*" has the same meaning as defined further above; R^{73} is hydrogen or $(\text{C}_1\text{--}\text{C}_2)\text{alkyl}$; and W^5 is selected from the moieties of partial Formulas (5.1.1) through (5.1.12), inclusive:

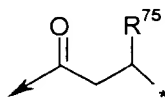
10



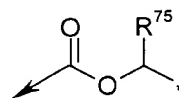
(5.1.1)



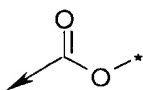
(5.1.2)



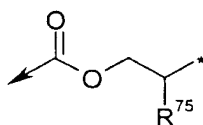
(5.1.3)



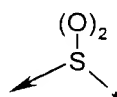
(5.1.4)



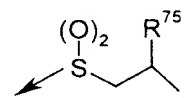
(5.1.5)



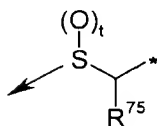
(5.1.6)



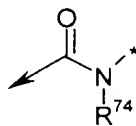
(5.1.7)



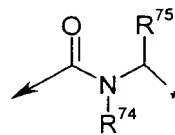
(5.1.8)



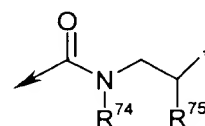
(5.1.9)



(5.1.10)



(5.1.11)



(5.1.12)

where the symbol: "→" indicates the point of attachment of the moiety W^5 represented

20 by partial Formulas (5.1.1) through (5.1.12) to the nitrogen atom in partial Formula (5.1.0), and the symbol: "*" indicates the point of attachment of the moiety W^5 to R^{77} . The substituents R^{74} and R^{75} are independently selected from hydrogen; $(\text{C}_1\text{--}\text{C}_2)\text{alkyl}$ substituted by 0 or 1 substituent independently selected from OH; and $(\text{C}_1\text{--}\text{C}_2)\text{alkoxy}$.

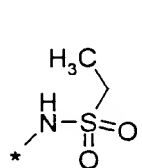
The group R^{77} may be selected from $(\text{C}_1\text{--}\text{C}_6)\text{alkyl}$; $(\text{C}_2\text{--}\text{C}_6)\text{alkenyl}$; and

25 $-(\text{CH}_2)_n\text{--}(\text{C}_3\text{--}\text{C}_7)\text{cycloalkyl}$, where n is 0, 1, or 2; and where said alkyl, alkenyl, alkynyl and cycloalkyl groups are substituted with 0 to 3 substituents R^{78} , where R^{78} is selected from oxo; -OH; $(\text{C}_1\text{--}\text{C}_2)\text{alkyl}$; $(\text{C}_1\text{--}\text{C}_3)\text{alkoxy}$; $-\text{CF}_3$; $-\text{C}(=\text{O})\text{OR}^{79}$; $-\text{C}(=\text{O})\text{NR}^{79}\text{R}^{80}$; $-\text{NR}^{79}\text{R}^{80}$;

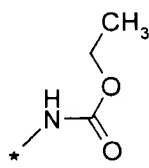
$-\text{NR}^{79}\text{C}(=\text{O})\text{R}^{80}$, $-\text{NR}^{79}\text{C}(=\text{O})\text{OR}^{80}$, $-\text{NR}^{79}\text{S}(=\text{O})_2\text{R}^{80}$, and $-\text{S}(=\text{O})_2\text{NR}^{79}\text{R}^{80}$, where R^{79} and R^{80} are each hydrogen or $(\text{C}_1-\text{C}_4)\text{alkyl}$.

Preferred groups of Formula 5.1.0 include ureas and amides. Carbamates are most preferred.

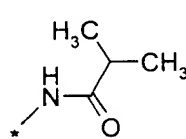
- 5 The alkyl and alkenyl groups comprising the moiety R^{77} preferably include such groups as methyl; ethyl; *iso*-propyl; *t*-butyl; and propenyl (allyl). These alkyl and alkenyl groups are substituted by 0 to 3 substituents R^{78} recited above. It is preferred that where a substituent is present that it be a single substituent selected from $-\text{OH}$; $-\text{CF}_3$; $-\text{CH}_3$; $-\text{OCH}_3$; and $-\text{NH}_2$. Consequently, groups of partial Formula (5.1.0) which are preferred embodiments of $\text{R}_{\text{region } \delta}$ include partial Formulas (5.1.15) through (5.1.22):



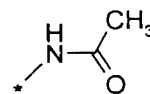
(5.1.15)



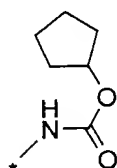
(5.1.16)



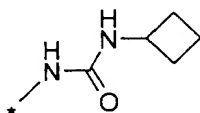
(5.1.17)



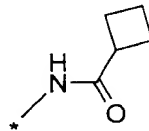
(5.1.18)



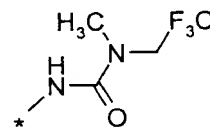
(5.1.19)



(5.1.20)

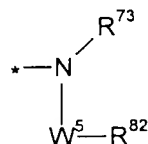


(5.1.21)



(5.1.22)

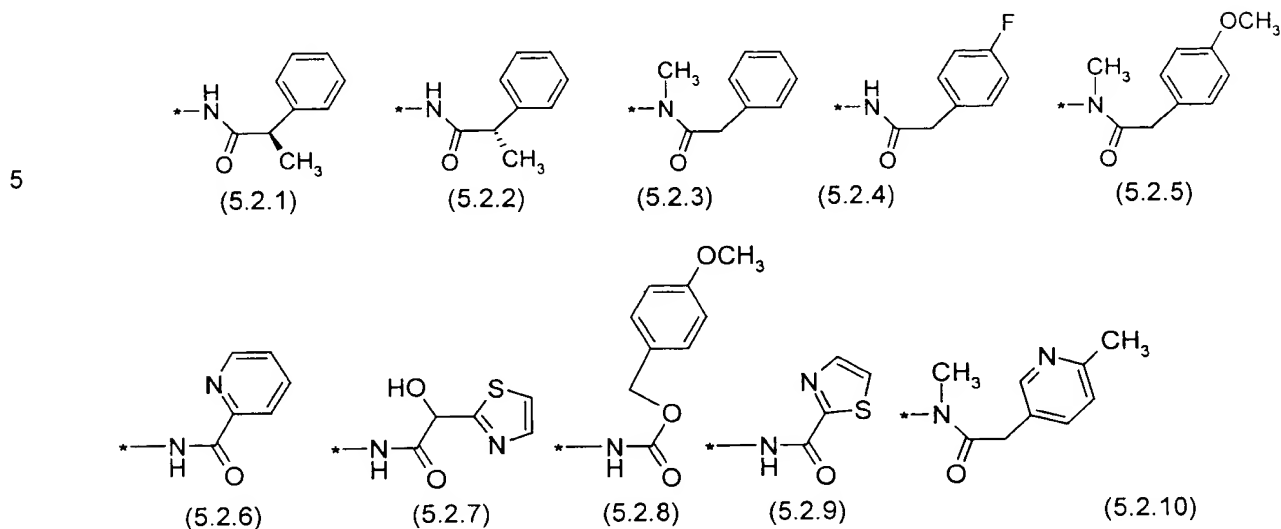
- 15 Another subclass of (substituted)-amide, carbamate, or urea moieties defining $\text{R}_{\text{region } \delta}$ includes aryl and heterocyclyl substituents. This second subclass comprises moieties of partial Formula (5.2.0):



(5.2.0)

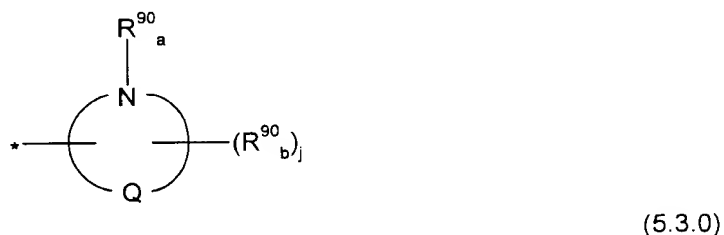
- 20 where the symbol: " \ast "; R^{73} ; and W^5 have the same meanings as under the definition of partial Formula (5.1.0) above; and under W^5 the symbol: " \ast " is as defined under the Formula (5.1.0). The group R^{82} is selected from phenyl; cinnolynyl; furyl; thienyl; pyrrolyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; imidazolyl; imidazolynyl; pyrazolyl; pyrazolynyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; indolyl; isoindolyl; indolynyl; benzo[*b*]furanyl; 2,3-dihydrobenzofuranyl; benzo[*b*]thiophenyl; 1H-indazolyl; benzimidazolyl; benzthiazolyl; quinolynyl; isoquinolynyl; phthalazinyl; quinazolynyl; and
- 25

quinoxaliny. The aryl or heterocyclyl groups comprising R^{82} may be substituted by 3 substituents R^{78} where R^{78} has the same meaning as defined above. Accordingly, preferred embodiments of the compounds of the present invention include partial Formulas (5.2.1) through (5.2.10):



Another class of moieties (under C.) defining $R_{\text{region } \delta}$ of the compounds of Formula (I) comprises two subclasses of (substituted)-heterocyclyl moieties. The first subclass (under C.2.) of such heterocyclyl moieties is selected from those of partial Formula (5.3.0):

10



where the symbol: "*" indicates the point of attachment of partial Formula (5.3.0) to $R_{\text{region } \gamma}$; Q is N, O or S; and R^{90}_a and R^{90}_b , are independently selected from the group consisting of hydrogen, $-(C_1-C_2)\text{alkylcarbonyl}$; $-(C_1-C_4)\text{alkyl}$; $-(CH_2)_n-(C_3-C_7)\text{cycloalkyl}$; $-(C_2-C_3)\text{alkenyl}$; $-(CH_2)_n(\text{phenyl})$; and $-(CH_2)_n(\text{HET}_2)$, where n is an integer selected from 0, 1, and 2. Further, j has the same meaning as above, but is selected independently. It is more preferred that j is 0, in which case the R^{90}_b substituent is absent. However, preferred embodiments of the present invention also include those wherein j is 1 and R^{90}_b is methyl.

15

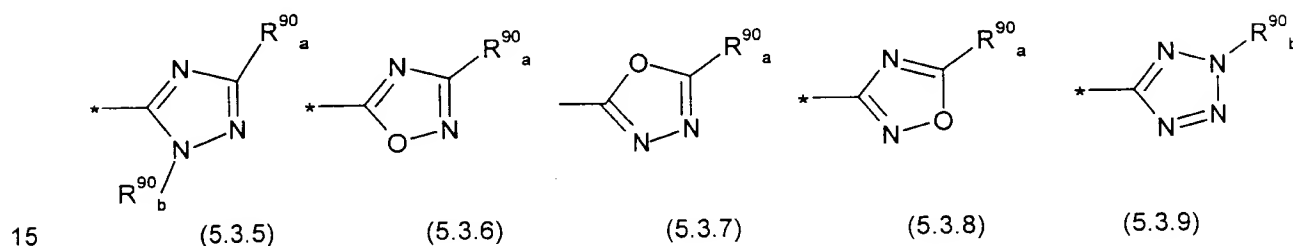
20

The heterocyclyl group HET_2 may be selected from the group consisting of thienyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; morpholinyl.

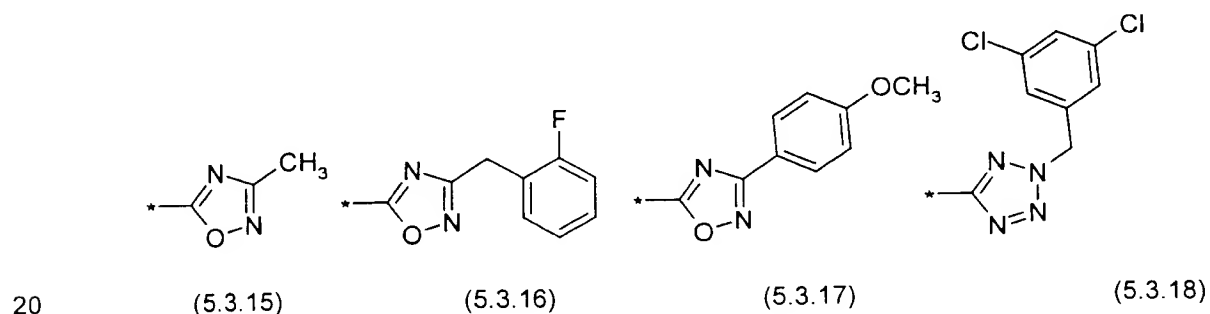
The above-mentioned alkyl, alkenyl, cycloalkyl, phenyl, and heterocyclyl groups are optionally substituted with up to 3 substituents R^{91} independently selected from the group consisting of F; Cl; $-C(=O)OR^{93}$; $-OH$; $-CN$; $C(=O)(C_1-C_4)alkyl$; $S(=O)_2(C_1-C_4)alkyl$; $-CONR^{93}R^{94}$; $-NR^{93}R^{94}$; $-NR^{93}C(=O)R^{94}$; $-NR^{93}C(=O)OR^{94}$; $-NR^{93}S(=O)_2R^{94}$; $-S(=O)_2NR^{93}R^{94}$; $(C_1-C_4)alkyl$ including dimethyl, and $(C_1-C_4)alkoxy$ each substituted with 1 to 3 substituents independently selected from F and Cl; $(C_1-C_2)alkoxycarbonyl$; $(C_1-C_2)alkylcarbonyl$; and $(C_1-C_2)alkylcarbonyloxy$, where R^{93} and R^{94} are each a member independently selected from the group consisting of hydrogen; and $(C_1-C_2)alkyl$.

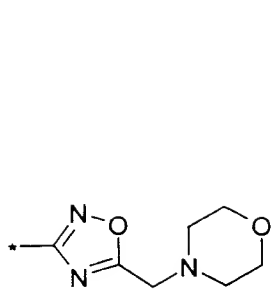
The heterocyclic group which constitutes a part of the moiety of partial Formula (5.3.0), may be a five membered monocyclic group containing two or more of N, O or S, for example oxazolyl; isoxazolyl; thiazolyl; iso-thiazolyl; triazolyl; triazinyl; tetrazolyl; oxadiazolyl; and thiadiazolyl.

Preferred embodiments include Formulas (5.3.5) through (5.3.9):

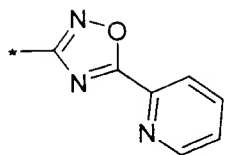


Accordingly, the following are preferred embodiments of the compounds of the present invention comprising moieties defining $R_{region \delta}$ in accordance with partial Formula (5.3.0), as represented by partial Formulas (5.3.15) through (5.3.26):

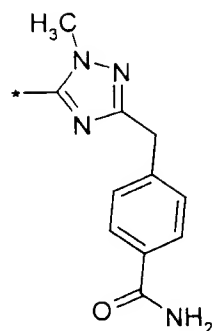




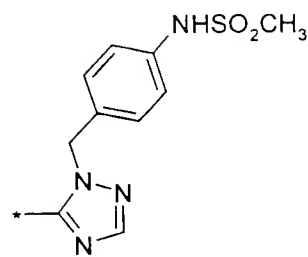
(5.3.19)



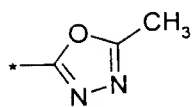
(5.3.20)



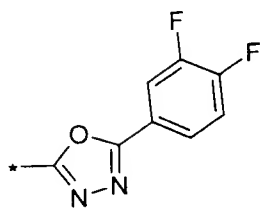
(5.3.21)



(5.3.22)



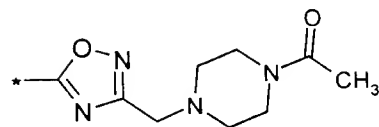
(5.3.23)



(5.3.24)

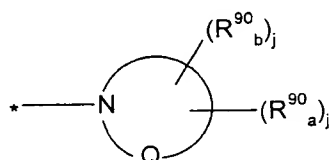


(5.3.25)



(5.3.26)

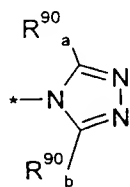
The second subclass of moieties (under C.2.) defining $R_{\text{region } \delta}$ may be selected from those of partial Formula (5.4.0):



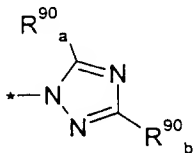
(5.4.0)

where Q , R^{90}_a and R^{90}_b have the same meaning as defined above, but are selected independently.

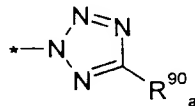
The heterocyclic group may be the same as in Formula 5.3.0 except that the nitrogen atom is the point of attachment. Accordingly, Formulas (5.4.5) through (5.4.8) result:



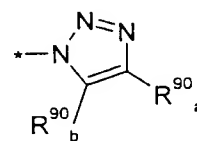
(5.4.5)



(5.4.6)

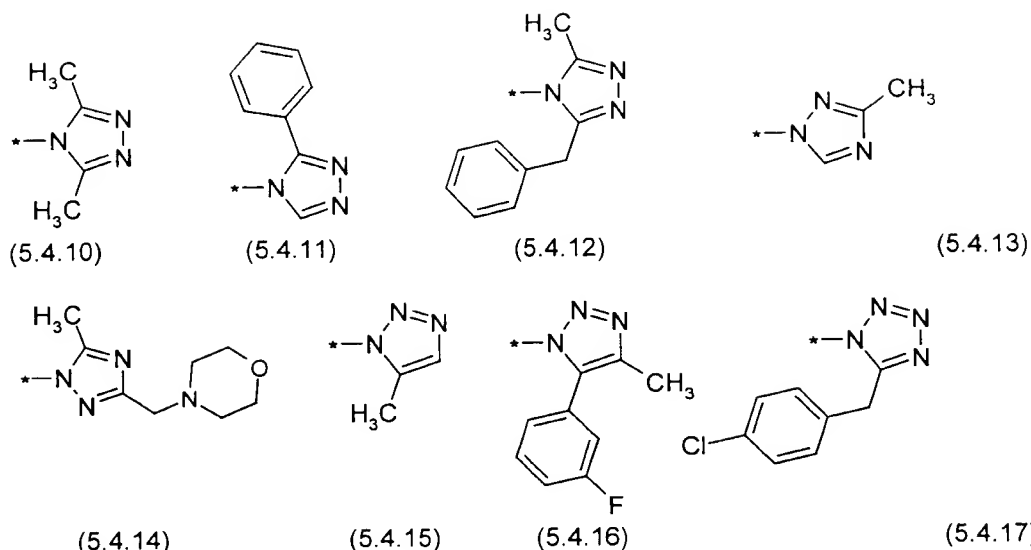


(5.4.7)



(5.4.8)

The following preferred embodiments of $R_{\text{region } \delta}$ are represented by partial Formulas (5.4.10) through (5.4.17):



5

The compounds of the present invention may be utilized in the form of acids, esters, or other chemical derivatives. It is also within the scope of the present invention to utilize those compounds in the form of pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures well known in the art.

10 The expression "pharmaceutically acceptable salt" as used herein is intended to mean an active ingredient comprising a compound of Formula (I) utilized in the form of a salt thereof, especially where said salt form confers on said active ingredient improved pharmacokinetic properties as compared to the free form of said active ingredient or other previously disclosed salt form.

15 A pharmaceutically acceptable salt form of said active ingredient may also initially confer a desirable pharmacokinetic property on said active ingredient which it did not previously possess, and may even positively affect the pharmacodynamics of said active ingredient with respect to its therapeutic activity in the body.

The pharmacokinetic properties of said active ingredient which may be favorably affected include, *e.g.*, the manner in which said active ingredient is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation or excretion of said active ingredient. While the route of administration of the pharmaceutical composition is important and various anatomical, physiological and pathological factors can critically affect bioavailability, the solubility of said active ingredient is

20 usually dependent upon the character of the particular salt form thereof which it utilized.

25 Further, an aqueous solution may provide the most rapid absorption of an active ingredient into the body of a patient being treated, while lipid solutions and suspensions, as well as solid

dosage forms, may result in less rapid absorption. Oral ingestion of said active ingredient is the most preferred route of administration for reasons of safety, convenience, and economy, but absorption of such an oral dosage form can be adversely affected by physical characteristics such as polarity, emesis caused by irritation of the gastrointestinal mucosa, 5 destruction by digestive enzymes and low pH, irregular absorption or propulsion in the presence of food or other drugs, and metabolism by enzymes of the mucosa, the intestinal flora, or the liver. Formulation of said active ingredient into different pharmaceutically acceptable salt forms may be effective in overcoming or alleviating one or more of the above-recited problems encountered with absorption of oral dosage forms.

10 Well-known pharmaceutically acceptable salts include, but are not limited to acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, besylate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecysulfate, ethanesulfonate, fumarate, glucoheptanoate, gluconate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2- 15 hydroxyethanesulfonate, isethionate, lactate, lactobionate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphonate, picrate, pivalate, propionate, salicylate, sodium phosphate, stearate, succinate, sulfate, sulfosalicylate, tartrate, thiocyanate, thiomalate, tosylate, and undecanoate.

20 Base salts of the compounds of the present invention include, but are not limited to ammonium salts; alkali metal salts such as sodium and potassium; alkaline earth metal salts such as calcium and magnesium; salts with organic bases such as dicyclohexylamine, meglumine, N-methyl-D-glucamine, tris-(hydroxymethyl)-methylamine (tromethamine), and salts with amino acids such as arginine, lysine, etc. Compounds of the present invention 25 which comprise basic nitrogen-containing groups may be quaternized with such agents as (C₁-C₄) alkyl halides, e.g., methyl, ethyl, *iso*-propyl and *tert*-butyl chlorides, bromides and iodides; di(C₁-C₄) alkyl sulfate, e.g., dimethyl, diethyl and diamyl sulfates; (C₁₀-C₁₈) alkyl halides, e.g., decyl, dodecyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aryl-(C₁-C₄) alkyl halides, e.g., benzyl chloride and phenethyl bromide. Such salts permit the 30 preparation of both water-soluble and oil-soluble compounds of the present invention.

Among the above-recited pharmaceutical salts those which are preferred include, but are not limited to acetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, 35 thiomalate, tosylate, and tromethamine.

Multiple salts forms are included within the scope of the present invention where a compound of the present invention contains more than one group capable of forming such pharmaceutically acceptable salts. Examples of typical multiple salt forms include, but are not limited to bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium, and trihydrochloride.

The compounds of this invention can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate or controlled release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose or milk sugar as well as high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the formula (I) can also be injected parenterally, for example, intravenously, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 1 microgram/kg to 25 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 0.05 mg to 1.0 g of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container or a nebuliser with the use of a suitable propellant, eg dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134a), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container or nebuliser may contain a solution or suspension of the active compound, eg using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, eg sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 20 µg to 20 mg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20 µg to 20 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) may also be transdermally administered by the use of a skin patch. They may also be administered by the ocular route, particularly for treating neurological disorders of the eye.

For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white

petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl
5 alcohol, 2-octyldodecanol, benyl alcohol and water.

The compounds of Formula (I) are described herein as possessing biological activity such that they are able to modulate CCR5 chemokine receptor activity and consequent or associated pathogenic processes subsequently mediated by the CCR5 receptor and its ligands. The expression "modulate CCR5 chemokine receptor activity" as used herein is
10 intended to refer to manipulation of the basic physiological processes and agencies which involve CCR5 chemokine receptors and their ligands. Included within the scope of this intended meaning are all types and subtypes of CCR5 receptors, in whatever tissues of a particular patient they are found, and in or on whatever components of the cells comprising those tissues they may be located. Most commonly, CCR5 receptors are situated on the cell
15 membranes of particular cell types such as monocytes. CCR5 receptors participate in and define, along with various endogenous ligands to which they are naturally bound, signaling pathways which control important cellular and tissue functions by means of the influence which they exert on the movement of agents such as the chemokines, into and out of those cells and tissues.

The basic functioning of the CCR5 receptors and their ligands may be modulated in a number of ways, and the scope of the present invention is not limited in that regard to any particular existing or hypothesized pathway or process. Thus, included within the intended meaning of modulation of CCR5 chemokine receptor activity, is the use of synthetically derived modulators introduced into a patient being treated, such as the compounds of
25 Formula (I) described herein. These exogenous agents may modulate CCR5 receptor activity by such well known mechanisms as competitive binding in which the natural ligands are displaced and their inherent functions disrupted. However, the present invention is not limited to any such specific mechanism or mode of action. Thus, "modulation" as used herein is intended to encompass preferably antagonism, but also agonism, partial antagonism and/or
30 partial agonism. Correspondingly, the term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought.

The term "patient" in this specification refers particularly to humans. However the compounds, methods and pharmaceutical compositions of the present invention may be used
35 in the treatment of animals.

Further included within the scope of the present invention are metabolites or residues of the compounds of Formula (I) which possess biological activity such that they are able to modulate CCR5 chemokine receptor activity and consequent or associated pathogenic processes subsequently mediated by the CCR5 receptor and its ligands. Once synthesized, the CCR5 chemokine receptor modulating activities and specificities of the compounds of Formula (I) according to the present invention may be determined using *in vitro* and *in vivo* assays which are described in detail further below.

The desirable biological activity of the compounds of Formula (I) may also be improved by appending thereto appropriate functionalities which enhance existing biological properties of the compound, improve the selectivity of the compound for the existing biological activities, or add to the existing biological activities further desirable biological activities. Such modifications are known in the art and include those which increase biological penetration into a given biological system, e.g., blood, the lymphatic system, and central nervous system; increase oral availability; increase solubility to allow administration by injection; alter metabolism; and alter the rate of excretion of the compound of Formula (I).

The dosage and dose rate of the compounds of Formula (I) effective for treating or preventing diseases and conditions in a patient which are mediated by or associated with modulation of CCR5 chemokine receptor activity as described herein, as well as for favorably affecting the outcome thereof in said patient, in accordance with the methods of treatment of the present invention comprising administering to said patient a therapeutically effective amount of a compound of Formula (I), will depend on a variety of factors such as the nature of the active ingredient, the size of the patient, the goal of the treatment, the nature of the pathology being treated, the specific pharmaceutical composition used, the concurrent treatments that the patient may be subject to, and the observations and conclusions of the treating physician.

Generally, however, the effective therapeutic dose of a compound of Formula (I) which will be administered to a patient will be between about 10 μ g (0.01 mg)/kg and about 60.0 mg/kg of body weight per day, preferably between about 100 μ g (0.1 mg)/kg and about 10 mg/kg of body weight per day, more preferably between about 1.0 mg/kg and about 6.0 mg/kg of body weight per day, and most preferably between about 2.0 mg/kg and about 4.0 mg/kg of body weight per day of the active ingredient of Formula (I).

Included within the scope of the present invention are embodiments comprising coadministration of, and compositions which contain, in addition to a compound of the present invention as active ingredient, additional therapeutic agents and active ingredients. Such multiple drug regimens, often referred to as combination therapy, may be used in the treatment and prevention of any of the diseases or conditions mediated by or associated with

CCR5 chemokine receptor modulation, particularly infection by human immunodeficiency virus, HIV. The use of such combinations of therapeutic agents is especially pertinent with respect to the treatment and prevention of infection and multiplication within a patient in need of treatment or one at risk of becoming such a patient, of the human immunodeficiency virus, HIV, and related pathogenic retroviruses. The ability of such retroviral pathogens to evolve within a relatively short period of time into strains resistant to any monotherapy which has been administered to said patient is well known in the technical literature.

In addition to the requirement of therapeutic efficacy which may necessitate the use of active agents in addition to the CCR5 chemokine receptor modulating compounds of Formula (I), there may be additional rationales which compel or highly recommend the use of combinations of drugs involving active ingredients which represent adjunct therapy, *i.e.*, which complement and supplement the function performed by the CCR5 chemokine receptor modulating compounds of the present invention. Such supplementary therapeutic agents used for the purpose of auxiliary treatment include drugs which, instead of directly treating or preventing a disease or condition mediated by or associated with CCR5 chemokine receptor modulation, treat diseases or conditions which directly result from or indirectly accompany the basic or underlying CCR5 chemokine receptor modulated disease or condition. For example, where the basic CCR5 chemokine receptor modulated disease or condition is HIV infection and multiplication, it may be necessary or at least desirable to treat opportunistic infections, neoplasms, and other conditions which occur as the result of the immune-compromised state of the patient being treated. Other active agents may be used with the compounds of Formula (I), *e.g.*, in order to provide immune stimulation or to treat pain and inflammation which accompany the initial and fundamental HIV infection.

Thus, the methods of treatment and pharmaceutical compositions of the present invention may employ the compounds of Formula (I) in the form of monotherapy, but said methods and compositions may also be used in the form of multiple therapy in which one or more compounds of Formula (I) are coadministered in combination with one or more known therapeutic agents such as those described in detail further herein.

The present invention also provides methods of treatment in which said pharmaceutical compositions are administered to a patient. Such methods relate to treating or preventing a disease or condition by modulating CCR5 chemokine receptor activity and consequent or associated pathogenic processes subsequently mediated by the CCR5 receptor and the active ligands with which it interacts or is bound. CCR5 and the other chemotactic cytokine, *i.e.*, chemokine, receptors, play a key role in the control of a number of processes which take place in the bodies of animals. Chemokine receptors, of which more than forty different species divided into four families are presently known to exist, are proteins

having a number of structural features in common, which act through chemical signaling. In the α family of chemokines, one amino acid (X) separates the first two cysteine residues, while in the β -chemokines the first two cysteine residues are adjacent to each other (C-C). Accordingly, these two families are identified as CXC and CC chemokines, respectively. The chemokines bind specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins called "chemokine receptors", named in accordance with the class of chemokines which they bind, followed by "R" and a number. Thus, "CCR5" is a C-C chemokine receptor. See Horuk, *Trends Pharm. Sci.*, **15**,159-165 (1994) for further details. CCR5 thus belongs to the β -chemokine receptor family, which is currently known to contain eight members, CCR1 through CCR8.

The CC type of chemokine receptor interacts with various signaling proteins, including the monocyte chemoattractant proteins, MCP-1, -2, -3, -4, and -5; eotaxin-1; macrophage inflammatory proteins MIP-1 α , and MIP-1 β ; and those regulated upon activation which are normal T-cell expressed and secreted, RANTES. The CCR5 type of chemokine receptor in particular is known to interact with MIP-1 α , MIP-1 β ; and RANTES in monocytes, activated T cells, dendritic cells, and natural killer cells. These β -chemokines do not act on neutrophils but rather attract monocytes, eosinophils, basophils, and lymphocytes with varying degrees of selectivity.

The present invention relates to compounds of Formula (I) which are useful in treating or preventing HIV infection, and to methods of treatment and pharmaceutical compositions containing such compounds as the active ingredient. It will be understood that the term "HIV" as used herein refers to human immunodeficiency virus (HIV), which is the etiological agent of AIDS (acquired immune deficiency syndrome), a disease that results in progressive destruction of the immune system and degeneration of the central and peripheral nervous system. Several HIV replication inhibitors are currently used as therapeutic or prophylactic agents against AIDS, and numerous others are presently under investigation.

In addition to cell-surface CD4, it has recently been shown that for entry into target cells, human immunodeficiency viruses require a chemokine receptor, CCR5 and CXCR-4 among others, as well as the virus's primary receptor CD4. The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-tropic strains of HIV-1 is CCR5, which as already mentioned, is a receptor for the β -chemokines RANTES, MIP-1 α and MIP-1 β . See Deng, *et al.*, *Nature*, **381**, 661-666 (1996) for a further description of CCR5 mediated HIV entry.

HIV attaches to the CD4 molecule on cells through a region of its envelope protein, gp120, and gp120 is part of a multi-subunit complex, most likely a trimer of gp160, *i.e.*, gp120 + gp41. It is believed that the CD4 binding site on the gp120 of HIV interacts with the CD4

molecule on the cell surface, triggering conformational changes across the trimer, which allow it to bind to another cell-surface receptor, such as CCR5. This in turn enables gp41 to induce fusion with the cell membrane, and entry of the viral core into the cell. In addition, macrophage-tropic HIV and SIV envelope proteins have been shown to induce a signal through CCR5 on CD4+ cells, which may enhance the replication of the virus. See Weissman, *et al.*, *Nature*, **389**, 981-985 (1997) for a description of this phenomenon. Further, it has been shown that a complex of gp120 and soluble CD4 interacts specifically with CCR5 and inhibits the binding of the natural CCR5 ligands, as described in Wu, *et al.*, *Nature*, **384**, 179-183 (1996); and Trkola, *et al.*, *Nature*, **384**, 184-187 (1996). It has further been demonstrated that β -chemokines and related molecules, e.g., (AOP)-RANTES, prevent HIV fusion to the cell membrane and subsequent infection, both *in vitro*, as described in Dragic, *et al.*, *Nature*, **381**, 667-673 (1996), and in animal models. Finally, absence of CCR5 appears to confer protection from HIV-1 infection, as described in *Nature*, **382**, 668-669 (1996). In particular, an inherited frame-shifting mutation in the CCR5 gene, $\Delta 32$, has been shown to abolish functional expression of the gene *in vitro*, and individuals homozygous for the mutation are apparently not susceptible to HIV infection, while at the same time they do not seem to be immuno-compromised by this variant. Furthermore, those heterozygote individuals that have been infected by HIV progress more slowly to full-blown clinical AIDS. In addition to validating the role of CCR5 in the infectious cycle of HIV, the above observations suggest that CCR5 is dispensable in the adult organism.

Although most HIV-1 isolates studied to date utilize CCR5 or CXCR-4, at least nine other chemokine receptors, or structurally related molecules, have also been described as supporting HIV-1 env-mediated membrane fusion or viral entry *in vitro*. These include CCR2b, CCR3, BOB/GPR15, Bonzo/STRL33/TYMSTR, GPR1, CCR8, US28, V28/CX3CR1, LTB-4, and APJ. There is good evidence that CCR3 can be used efficiently by a significant fraction of HIV-1 isolates *in vitro*, provided that this protein is over-expressed in transfected cells. Nevertheless, consistent evidence indicates that anti-HIV drugs targeted to chemokine receptors may not be compromised by this variability. Indeed, the chemokines RANTES, MIP-1 α , MIP-1 β , SDF-1 have been shown to suppress replication of primary HIV isolates. A derivative of RANTES, (AOP)-RANTES, is a sub-nanomolar antagonist of CCR5 function in monocytes. Monoclonal antibodies to CCR5 have been reported to block infection of cells by HIV *in vitro*. A small molecule antagonist of CXCR4, identified as AMD3100, has been reported to inhibit infection of susceptible cultures by CXCR4 dependent primary and lab-adapted HIV viruses while another small molecule called TAK 779 blocks entry of CCR5-tropic strains (Baba, *et al.* *PNAS*, **96** (10), 5698-5703 (1999); In addition, the majority of primary strains from early and late disease stages utilize CCR5 exclusively or in addition to other chemokine receptors, indicating that CCR5 dependent infection may play an essential role in

the initiation and maintenance of productive HIV infection in a host. Accordingly, an agent which blocks CCR5 in patients including mammals, and especially humans who possess normal chemokine receptors, can reasonably be expected to prevent infection in healthy individuals and slow or halt viral progression in infected patients.

5 Accordingly, the present invention is directed to the compounds of Formula (I) which inhibit the entry of human immunodeficiency virus into target cells and are therefore of value in the prevention and/or treatment of infection by HIV, as well as the prevention and/or treatment of the resulting acquired immune deficiency syndrome (AIDS). Evidence can be produced which is probative of the fact that the compounds of Formula (I) described herein inhibit viral
10 entry through selective blockade of CCR5 dependent fusion. Consequently, the present invention also relates to pharmaceutical compositions containing the compounds of Formula (I) as an active ingredient, as well as to the corresponding method of use of the compounds of Formula (I) as stand-alone agents, or in conjunction with other agents for the prevention and treatment of infection by HIV and resulting AIDS.

15 The utility of the compounds of Formula (I) of the present invention as inhibitors of HIV infection may be demonstrated by any one or more methodologies known in the art, such as the HIV microculture assays described in Dimitrov *et al.*, *J. Clin. Microbiol.* **28**, 734-737 (1990)), and the pseudotyped HIV reporter assay described in Connor *et al.*, *Virology* **206** (2) 935-44 (1995). In particular, specific compounds of Formula (I) disclosed herein as preferred
20 embodiments are shown to inhibit p24 production following replication of laboratory-adapted and primary HIV strains in primary blood lymphocytes (PBLs) and clonal cell-lines known to support replication of both CCR5 and CXCR-4 tropic viruses, *e.g.*, PM-1 and MOLT4-clone 8. It is also noted that only those viral strains known to use CCR5 are shown to be inhibited, whereas replication of CXCR-4 tropic viruses is shown to be unaffected, indicating that
25 compounds of Formula (I) disclosed herein are able to prevent viral entry through selective blockade of CCR5 dependent fusion. Furthermore, compounds of Formula (I) are shown to inhibit entry of chimeric HIV reporter viruses pseudotyped with envelope from a CCR5 dependent strain (ADA). Finally, compounds of Formula (I) are shown to inhibit infection of primary cells by HIV isolated from infected patient blood. Further confirmation of this anti-HIV
30 mechanism is provided by experiments outlined below.

 The ability of the compounds of Formula (I) to modulate chemokine receptor activity is demonstrated by methodology known in the art, such as the assay for CCR5 binding following procedures disclosed in Combadiere *et al.*, *J. Leukoc. Biol.* **60**, 147-52 (1996); and/or intracellular calcium mobilisation assays as described by the same authors. Cell lines
35 expressing the receptor of interest include those naturally expressing the receptor, such as PM-1, or IL-2 stimulated peripheral blood lymphocytes (PBL), or a cell engineered to express

a recombinant receptor, such as CHO, 300.19, L1.2 or HEK-293. In particular, the compounds of Formula (I) disclosed herein are shown to have activity in preventing binding of all known chemokine ligands to CCR5 in the above-mentioned binding assays. In addition, the compounds of Formula (I) disclosed herein are shown to prevent intracellular calcium mobilization in response to endogenous agonists, which is consistent with their functioning as CCR5 antagonists. For the treatment of infection by HIV and the prevention and/or treatment of the resulting acquired immune deficiency syndrome (AIDS), compounds of Formula (I) which are shown to be antagonists are preferred to compounds of Formula (I) which are shown to be agonists.

10 The present invention in one of its preferred embodiments is directed to the use of the compounds of Formula (I) disclosed herein for the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment and/or delaying of the onset of consequent pathological conditions, including but not limited to AIDS. The expressions "treating or preventing AIDS", and "preventing or treating infection by HIV" as
15 used herein are intended to mean the treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. The quoted expressions are not intended, however, to be limited to the recited treatments, but rather are contemplated to include all beneficial uses relating to conditions attributable to an AIDS causative agent. For example, the compounds of Formula
20 (I) are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, sexual intercourse, bites, needle stick, or exposure to patient blood. In addition, a compound of Formula (I) may be used for the prevention of infection by HIV and the prevention of AIDS, such as in pre-or post-coital prophylaxis or in the prevention of maternal transmission of the HIV virus to a fetus or a child,
25 whether at the time of birth, during the period of nursing, or in any other manner as above-described.

In a preferred embodiment of the present invention, a compound of Formula (I) may be used in a method of inhibiting the binding of human immunodeficiency virus to a chemokine receptor such as CCR5, which comprises contacting the target cell with a
30 therapeutically effective amount of a compound of Formula (I) which is effective to inhibit the binding of the virus to the chemokine receptor. The subject treated by these preferred methods of the present invention is a mammal, preferably a human, male or female, in whom modulation of chemokine receptor activity is desired and contemplated to be efficacious. As already pointed out, the term "modulation" as used herein is intended to encompass preferably
35 antagonism, but also agonism, partial antagonism and/or partial agonism. Also, the expression "therapeutically effective amount" as used herein is intended to mean the amount

of a compound of Formula (I) as disclosed herein that will elicit the biological or medical response of a tissue, system, or animal, especially human that is being sought.

In another preferred embodiment of the present invention, a compound of Formula (I) may be used to evaluate putative retrovirus, especially HIV, mutants considered to be resistant to anti-HIV therapeutic agents, including the compounds of Formula (I) disclosed herein. Mutant viruses may be isolated from *in vitro* cultures by methods known in the art, but may also be isolated from *in vivo* animal infection models which have been disclosed in the art. More significantly, mutant viruses may be isolated from samples of patients undergoing treatment, whether optimal or sub-optimal, comprising administration of a compound of Formula (I), or any combination thereof with other known or to-be-discovered therapeutic agents. Such mutant viruses or their components, particularly their envelope proteins, may be used for several advantageous purposes, including but not limited to the following: (i) the evaluation and/or development of novel chemokine modulators or other agents having improved activity against such mutant viruses; and (ii) the development of diagnostics capable of assisting physicians or other clinicians in the choice of a therapeutic regimen and/or outcome prediction for a patient.

In a further preferred embodiment of the present invention, compounds of Formula (I) disclosed herein are used as tools for determining the co-receptor affinity of retroviruses including HIV and SIV, or their components, especially their envelope proteins. This affinity data can be used for several advantageous purposes, including but not limited to phenotyping a given viral population, *e.g.* prior to administration of anti-retroviral therapy. The affinity data may also be used to predict the progression and outcome of the infection by the virus population involved.

In another preferred embodiment of the present invention, a compound of Formula (I) is used in the preparation and execution of screening assays for compounds which modulate the activity of chemokine, especially CCR5 receptors. For example, compounds of Formula (I) as disclosed herein are useful for isolating receptor mutants, which can then be made into screening tools for the discovery of even more potent compounds, following procedures well known in the art. Furthermore, the compounds of Formula (I) are useful in establishing or characterizing the binding sites of other ligands, including compounds other than those of Formula (I) and viral envelope proteins, to chemokine receptors, *e.g.*, by competitive inhibition. The compounds of Formula (I) are also useful for the evaluation of putative specific modulators of various chemokine receptors. As will be appreciated by the artisan, thorough evaluation of specific agonists and antagonists of the above-described chemokine receptors has been hampered by the lack of non-peptidyl, *i.e.*, metabolically resistant compounds with

high binding affinity for these receptors. Thus, the compounds of Formula (I) are useful as products which may be commercially exploited for these and other beneficial purposes.

Included within the scope of the present invention are combinations of the compounds of Formula (I) with one or more therapeutic agents useful in the prevention or treatment of AIDS. For example, the compounds of the present invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure to HIV, in combination with therapeutically effective amounts of known AIDS antivirals, immunomodulators, anti-infectives, or vaccines familiar to those skilled in the art. It will be understood that the scope of such combinations which include the compounds of Formula (I) is not limited to the above-recited list, but includes as well any combination with another pharmaceutically active agent which is useful for the prevention or treatment of HIV and AIDS.

Preferred combinations of the present invention include simultaneous, or sequential treatments with a compound of Formula (I) and one or more inhibitors of HIV protease and/or inhibitors of HIV reverse transcriptase, preferably selected from the class of non-nucleoside reverse transcriptase inhibitors (NNRTI), including but not limited to nevirapine, delavirdine, and efavirenz; from among the nucleoside/nucleotide inhibitors, including but not limited to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and adefovir dipivoxil; and from among the protease inhibitors, including but not limited to indinavir, ritonavir, saquinavir, nelfinavir, and amprenavir. Other agents useful in the above-described preferred embodiment combinations of the present invention include current and to-be-discovered investigational drugs from any of the above classes of inhibitors, including but not limited to FTC, PMPA, fozivudine tidoxil, talviraline, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, and KNI-764. There is also included within the scope of the preferred embodiments of the present invention, combinations of a compound of Formula (I) together with a supplementary therapeutic agent used for the purpose of auxiliary treatment, wherein said supplementary therapeutic agent comprises one or more members independently selected from the group consisting of proliferation inhibitors, e.g., hydroxyurea; immunomodulators, e.g., sargramostim, and various forms of interferon or interferon derivatives; fusion inhibitors, e.g., AMD3100, T-20, PRO-542, AD-349, BB-10010 and other chemokine receptor agonists/antagonists; integrase inhibitors, e.g., AR177; RNaseH inhibitors; inhibitors of viral transcription and RNA replication; and other agents that inhibit viral infection or improve the condition or outcome of HIV-infected individuals through different mechanisms.

Preferred methods of treatment of the present invention for the prevention of HIV infection, or treatment of aviremic and asymptomatic subjects potentially or effectively infected with HIV, include but are not limited to administration of a member independently selected

from the group consisting of: (i) a compound within the scope of Formula (I) as disclosed herein; (ii) one NNRTI in addition to a compound of (i); (iii) two NRTI in addition to a compound of (i); (iv) one NRTI in addition to the combination of (ii); and (v) a compound selected from the class of protease inhibitors used in place of an NRTI in combinations (iii) and (iv).

The preferred methods of the present invention for therapy of HIV-infected individuals with detectable viremia or abnormally low CD4 counts further include as a member to be selected: (vi) treatment according to (i) above in addition to the standard recommended initial regimens for the therapy of established HIV infections, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0. Such standard regimens include but are not limited to an agent from the class of protease inhibitors in combination with two NRTIs; and (vii) a standard recommended initial regimens for the therapy of established HIV infections, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0), where either the protease inhibitor component, or one or both of the NRTIs is/are replaced by a compound within the scope of Formula (I) as disclosed herein.

The preferred methods of the present invention for therapy of HIV-infected individuals that have failed antiviral therapy further include as a member to be selected: (viii) treatment according to (i) above, in addition to the standard recommended regimens for the therapy of such patients, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0); and (ix) a standard recommended initial regimens for the therapy of patients who have failed antiretroviral therapy, e.g., as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0), where either one of the protease inhibitor components, or one or both of the NRTIs is/are replaced by a compound within the scope of Formula (I) as disclosed herein.

In the above-described preferred embodiment combinations of the present invention, the compound of Formula (I) and other therapeutic active agents may be administered in terms of dosage forms either separately or in conjunction with each other, and in terms of their time of administration, either serially or simultaneously. Thus, the administration of one component agent may be prior to, concurrent with, or subsequent to the administration of the other component agent(s).

The compounds of Formula (I) may be administered in accordance with a regimen of 1 to 4 times per day, preferably once or twice per day. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of

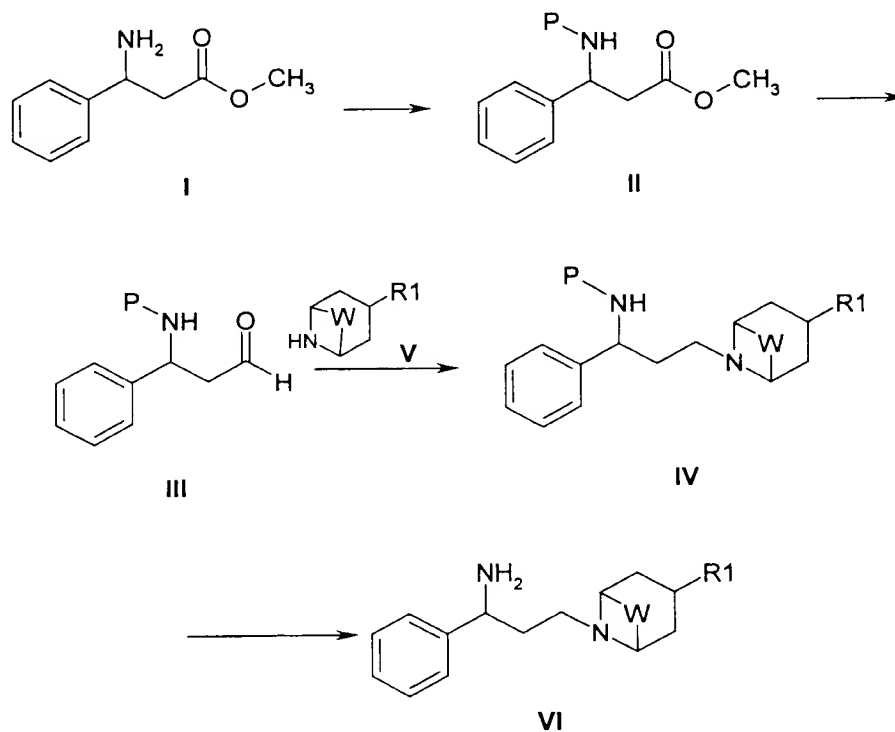
action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. In particular, however, the treatment of retroviral infections, and more particularly HIV, may be guided by genotyping and phenotyping the virus in the course of or prior to the initiation of administration of the therapeutic agent. In this way, it is possible to optimise dosing regimens and efficacy when administering a compound of Formula (I) for the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV).

The compounds of this invention may be used for treatment of respiratory disorders, including: adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis.

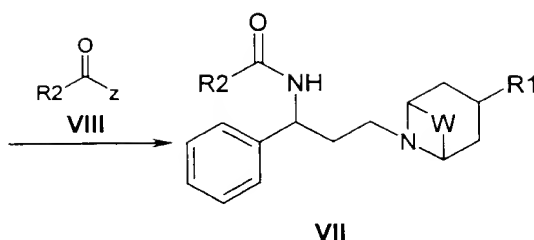
The invention is further described by means of examples, but not in any limitative sense.

The following synthetic routes were employed.

15

Synthesis I

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Preparation of the compounds of formula II from the amino acid derivative I where P is a suitable protecting group (preferably BOC), may be achieved for example, by reaction with di-tert-butyl dicarbonate in the presence of a base such as aqueous sodium hydroxide in a suitable solvent such as tetrahydrofuran.

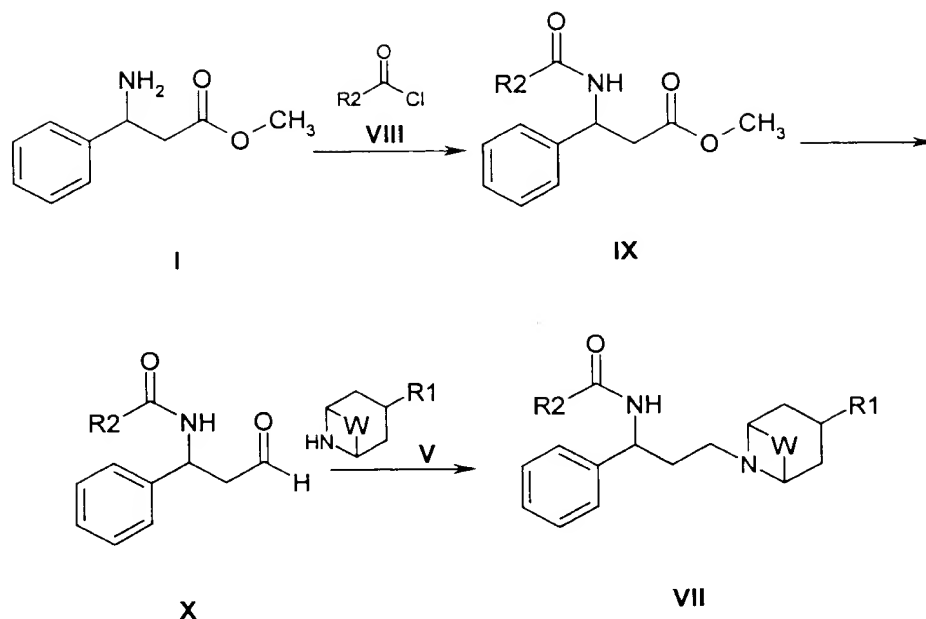
Compounds of formula III may be prepared by reduction of compounds of formula II, using a suitable reducing agent, preferably diisobutylaluminium hydride in dichloromethane at -78°C.

Compounds of the general formula IV may be prepared by the reductive alkylation of an appropriate amine of formula V, with an aldehyde, of formula III. The reaction may be carried out in the presence of an excess of suitable reducing agent (eg. sodium triacetoxyborohydride) in a protic solvent system (acetic acid in dichloromethane or 1,1,1-trichloroethane), at room temperature.

Subsequent removal of the nitrogen protecting group may be achieved using trifluoroacetic acid or hydrochloric acid in a solvent such as dioxan or dichloromethane at room temperature for from 1 to 60 hours to provide the compound of formula VI. Compounds of general formula VII may be prepared by coupling the amine of formula VI with an acid (Z = OH) or acid derivative (eg, Z = Cl) of formula VIII using conventional amide bond forming techniques. For example, the acid VIII may be activated using a carbodiimide such as 3-(3-dimethylamino-1-propyl)-1-ethylcarbodiimide, optionally in the presence of 1-hydroxybenzotriazole hydrate. These reactions may be performed in a suitable solvent such as dichloromethane, optionally in the presence of a tertiary amine, such as triethylamine or N-ethyldiisopropylamine at about room temperature.

Alternatively an acyl chloride of formula VIII, may be reacted with an amine of formula VI in the presence of a tertiary amine, such as triethylamine or N-ethyldiisopropylamine in a suitable solvent such as dichloromethane at room temperature for about 3 hours.

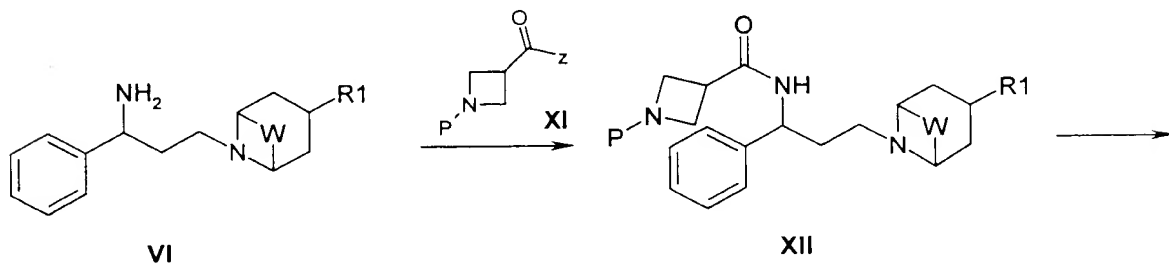
In a further variation a compound of formula VII, may be formed in a "one-pot procedure" by deprotection of a compound of formula IV, and coupling the resultant amine of formula VI with the acid derivative of formula VIII, using methods previously described.

Synthesis II

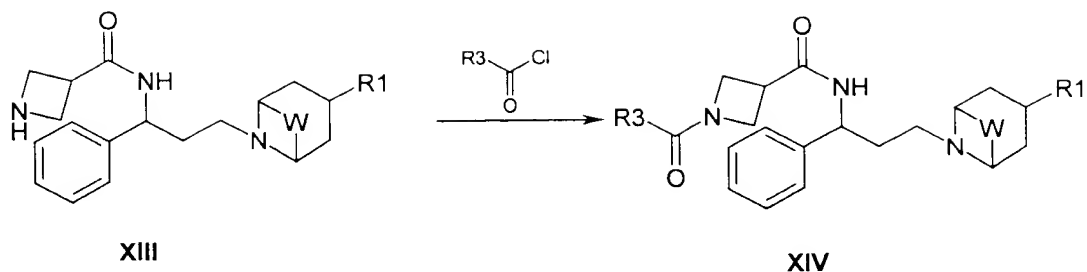
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Compounds of formula **IX** may be prepared by coupling the amino acid derivative of formula **I** with an acid chloride of formula **VIII** in the presence of a tertiary amine, such as triethylamine, in a suitable solvent, such as dichloromethane at between 0°C and room temperature. Compounds of formula **X** may be prepared by reduction of compounds of formula **IX**, according to the method described in synthesis I. Reductive alkylation of the amine of formula **V**, with the aldehyde of formula **X**, according to the method described in synthesis I, may provide the compounds of formula **VII**.

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Synthesis III

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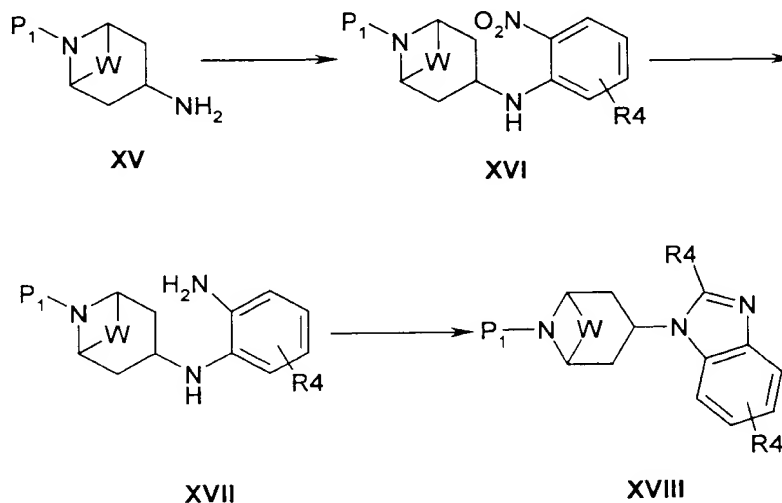


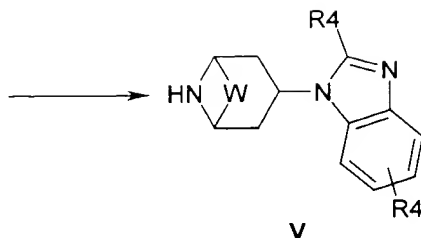
Compounds of the general formula **XII** may be prepared by coupling the amine of formula **VI** with the protected amino acid derivative of formula **XI** (where Z = Cl or OH and P is preferably BOC or benzyl), using methods previously described in synthesis I. Removal of the nitrogen protecting group, using standard methodology provides the compound of formula **XIII**. Typically, removal of a CBz protecting group may be achieved under catalytic hydrogenation conditions using a catalyst such as Pearlman's catalyst, in the presence of an excess of ammonium formate, in a suitable solvent such as ethanol under reflux conditions.

Compounds of formula **XIV** may be obtained by coupling the amine of formula **XIII** with an appropriate acyl chloride, using methods previously described in synthesis II.

Alternatively, a compound of formula **XIV** may be formed in a "one-pot procedure", by deprotection of the nitrogen group, and coupling the resultant intermediate with an acyl chloride as described above.

Synthesis IV



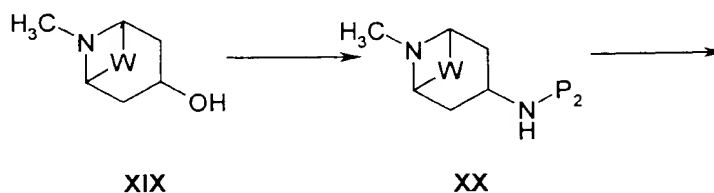


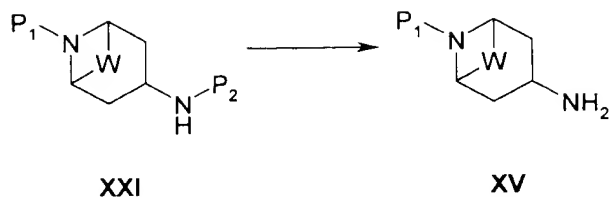
Compounds of formula **XVI** may be prepared by the alkylation of amines of formula **XV** using a suitable alkylating agent, preferably 2-fluoronitrobenzene, in the presence of an excess of a suitable base, typically potassium carbonate, in a solvent such as N,N-dimethylformamide at between 100°C and 140°C for about 2 to 18 hours. Compounds of formula **XVII** may be prepared by reduction of the corresponding compounds of formula **XVI**. This reduction may be performed under a variety of reaction conditions, for example by catalytic hydrogenation (10% palladium on charcoal, in a solvent such as ethyl acetate, optionally in the presence of an alcohol, such as methanol, at 1 atm. H₂ pressure and room temperature) or by transition metal catalysed reduction (at reflux temperature in the presence of an excess of iron powder in acetic acid, or iron powder and calcium chloride in aqueous ethanol, or an excess of tin chloride dihydrate in ethanol, for about 2 hours). It will be appreciated by those skilled in the art, that when P₁ is acid labile (eg BOC) the conditions required for transition metal catalysed reduction may also result in the simultaneous deprotection of the nitrogen group.

Compounds of formula **XVIII** may be prepared by the condensation of the amine of formula **XVII** and an appropriate orthoester under reflux conditions, optionally in the presence of acid catalysis, (eg hydrochloric acid or p-toluenesulphonic acid).

Deprotection of the nitrogen protecting group (when necessary) to yield the amine of formula **V** may be accomplished using the method of Genêt et al (Tet. Lett. 36; 8; 1267, 1995) or by using methods as previously described above.

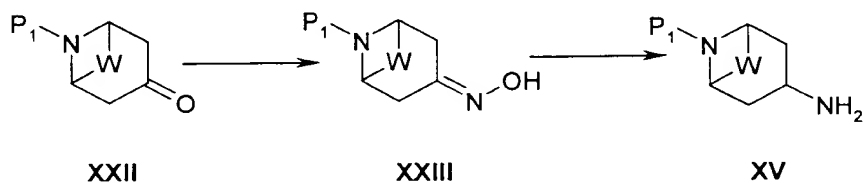
Synthesis V





The amine of formula **XX** may be prepared from the alcohol of formula **XIX** by reaction with a protected amine, (P_2NH_2), for example phthalimide, according to the method of Mitsunobu (Org. React. 1992; 42; 335). The compound of formula **XXI** may be prepared by a concerted demethylation and protection of the amine of formula **XX**. Typically this is achieved using a large excess of ethyl chloroformate, in a suitable solvent such as toluene, at about 90°C. Deprotection of the nitrogen (P_2) of the compound of formula **XXI** using for example, hydrazine hydrate, in a suitable solvent such as ethanol at reflux temperature provided the amine of formula **XV**.

Synthesis VI

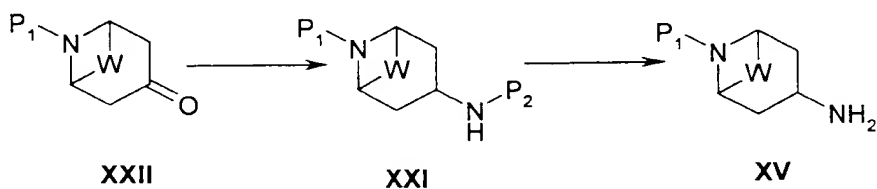


15

Oximes of general formula **XXIII** may be prepared by the condensation of compounds of general formula **XII** with hydroxylamine hydrochloride, in the presence of a base such as pyridine, and in a suitable solvent, typically ethanol, at reflux temperature for about 2 hours. Reduction of the compounds of formula **XXIII** may be achieved using sodium in the presence of an alcohol, typically pentanol, to provide the amine of formula **XV**.

20

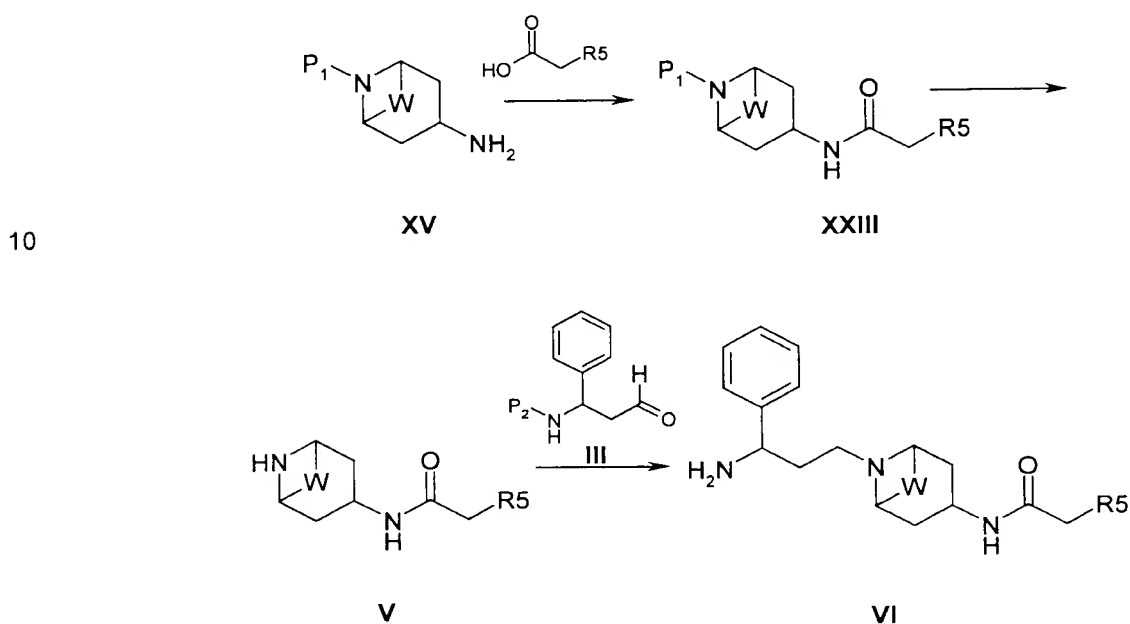
Synthesis VII



25

The nitrogen protected diamine of formula **XXI** may alternatively be prepared by reaction of the ketone of formula **XXII** with a protected amine (preferably benzyl) using reductive amination methodology, as previously described in synthesis I. Deprotection of this benzyl group typically using catalytic hydrogenation conditions using palladium on charcoal as a catalyst in a suitable solvent such as ethyl acetate at 1 atm of H₂ pressure at between about room temperature and 50°C, provides the amine of formula **XV**.

Synthesis VIII



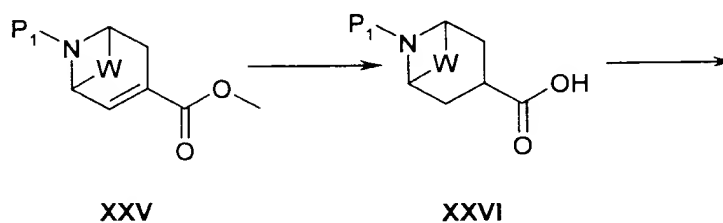
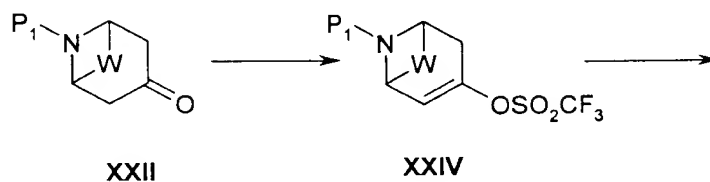
Compounds of the formula **XXIII**, may be prepared by coupling the protected amine of formula **XV** (P_1 is for example, BOC or Benzyl) with a carboxylic acid of formula (R_5CH_2COOH) . The coupling may be achieved using conventional amide bond forming techniques, as described in synthesis I. For example the acid may be activated using a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide in the presence of 1-hydroxybenzotriazole in a suitable solvent such as dichloromethane, in the presence of a tertiary amine such as diisopropylamine. Compounds of formula **V** may be prepared by nitrogen deprotection of compounds of formula **XXIII**, using techniques previously described above. Compounds of formula **VI** may be prepared by the reductive amination of amines of formula **V** with an appropriate aldehyde of formula **III**. The reaction may be carried out in the presence of a suitable reducing agent (eg sodium triacetoxyborohydride) in a protic solvent

15

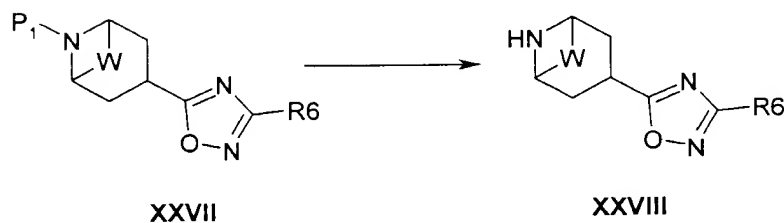
20

system (eg acetic acid, dichloromethane). Deprotection of the nitrogen using standard methodology as previously described, provides the compounds of general formula VI.

5

Synthesis IX

10



Compounds of formula **XXIV** may be prepared from the carbonyl compounds of formula **XXII**, by treatment initially with a suitable base such as lithium diisopropylamine at -78°C, and quenching the resultant anion with an appropriate electrophilic triflate, such as N-(5-chloro-2-pyridyl)triflimide, in a solvent, such as tetrahydrofuran, according to the method of Comins (Tet. Lett. 33; 6299; 1992).

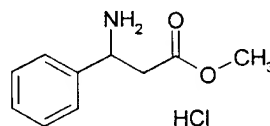
Compounds of formula **XXV** may be prepared from compounds of formula **XXIV**, by palladium catalysed functionalisation of the vinyl triflate group. For example, treatment of compound **XXIV** with a palladium catalyst (prepared in-situ from palladium acetate and triphenylphosphine) in the presence of a suitable base such as triethylamine, in a mixture of DMF and methanol, under an atmosphere of carbon monoxide gives compounds of formula **XXV**.

Compounds of formula **XXVI** may be prepared in a "one-pot", two-step procedure from compounds of formula **XXIV**. Reduction of the double bond under hydrogenation conditions, typically using a catalyst such as Raney® Nickel, in an alcohol (eg methanol), at 60psi of H₂ pressure and room temperature. Hydrolysis of the intermediate alkyl ester, according to the plethora of methods currently available yielded compounds of formula **XXVI**. For example, treatment with sodium hydroxide in a mixture of tetrahydrofuran and water at room temperature. Compounds of formula **XXVII** may be prepared by coupling the acid of formula **XXVI** with an appropriate oxime, followed by in-situ cyclocondensation. For example, the acid may be activated using a fluorinating agent, such as N,N,N',N'-bis(tetramethylene)fluoroformamidinium hexafluorophosphate (J.A.C.S. 1995; 117(19); 5401) in the presence of a base such as N-ethyldiisopropylamine in a suitable solvent such as dichloromethane at room temperature. Cyclocondensation of the resultant intermediate may subsequently be achieved by heating in an appropriate solvent such as dioxan at elevated temperature (eg 130°C) for about 3 hours.

Deprotection of the nitrogen group (typically BOC) of compounds of formula **XXVII** using standard methodology such as protonolysis using hydrochloric acid, according to the methods previously described, affords compounds of formula **XXVIII**.

PREPARATION 1

Methyl 3-amino-3-phenylpropanoate hydrochloride

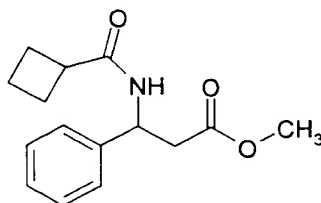


3-Phenyl-β-alanine (13.0g, 78.8mmol) was dissolved in methanolic hydrochloric acid (200ml, 2.25M). The reaction was heated under reflux for 18 hours, then the cooled mixture was concentrated under reduced pressure to afford the title compound as a yellow oil, 16.9g.

¹H-NMR (400MHz, CD₃OD) : δ [ppm] 3.00-3.19 (2H, m), 3.72 (3H, s), 4.74 (1H, t), 7.48 (5H, s).

PREPARATION 2

Methyl 3-[(cyclobutylcarbonyl)amino]-3-phenylpropanoate



Cyclobutanecarbonyl chloride (6.91ml, 86.7mmol) was added dropwise to a solution of the title compound of preparation 1 (16.9g, 78.8mmol) and triethylamine (24.2ml, 173.4mmol) in dichloromethane (200ml) at 0°C. The reaction mixture was stirred for 56 hours at room temperature after which time the mixture was washed with water, then brine, dried (MgSO₄), filtered and the solvent removed under reduced pressure to afford the title compound as a yellow oil, 20.8g.

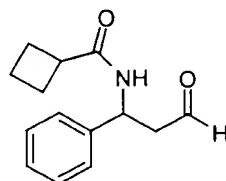
¹H-NMR (400MHz, CDCl₃) : δ [ppm] 2.00-2.10 (2H, m), 2.10-2.35 (4H, m), 2.80-3.00 (2H, m), 3.03 (1H, m), 3.62 (3H, s), 5.42 (1H, m), 6.50 (1H, d), 7.25-7.35 (5H, m).

LRMS : m/z 262 (MH⁺)

10

PREPARATION 3

N-(3-Oxo-1-phenylpropyl)cyclobutanecarboxamide



Diisobutylaluminium hydride (42.1ml of a 1.0M solution in dichloromethane, 42.1mmol) was added dropwise to a solution of the title compound of preparation 2 (5.0g, 19.1mmol) in dichloromethane (100ml) at -78°C. The reaction mixture was stirred at this temperature for an hour, then methanol (5ml) pre-cooled to -78°C was added. The mixture was warmed to room temperature and washed with 2N hydrochloric acid, water, brine, dried (MgSO₄), filtered and the solvent evaporated under reduced pressure to afford the title compound as a yellow oil, 3.3g.

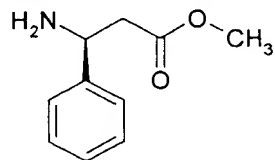
¹H-NMR (400MHz, CDCl₃) : δ [ppm] 1.81-2.35 (6H, m), 2.90-3.10 (3H, m), 5.50 (1H, m), 6.00 (1H, bd), 7.23-7.39 (5H, m), 9.75 (1H, m).

LRMS : m/z 232 (MH⁺)

25

PREPARATION 4

Methyl (3S)-3-amino-3-phenylpropanoate



A solution of *tert*-butyl (3S)-3-amino-3-phenylpropanoate (5.04g, 22.9mmol) in 2.25M methanolic hydrochloric acid (100ml) was heated under reflux for 2 ½

hours. The mixture was cooled to room temperature, basified with saturated sodium carbonate solution to pH 8 and the phases separated. The aqueous layer was extracted with dichloromethane (4x), the combined organic solutions were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound, 3.97g.

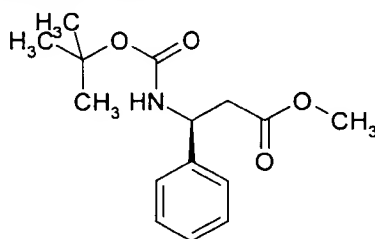
5 $^1\text{H-NMR}$ (400MHz, CDCl_3) : δ [ppm] 1.70 (2H, s), 2.66 (2H, d), 3.68 (3H, s), 4.43 (1H, t), 7.25-7.40 (5H, m).

LRMS: m/z 180.3 (MH^+).

PREPARATION 5

10

Methyl (3S)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate



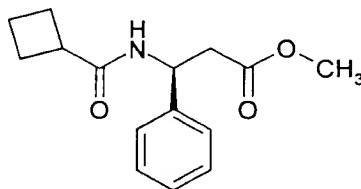
The title compound from preparation 4 (5.38g, 30mmol) and di-*tert*-butyl dicarbonate (8.72g, 40mmol) in tetrahydrofuran (50ml) and 2N sodium hydroxide solution (25ml) were stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, the layers separated and the aqueous phase extracted with ethyl acetate (2x). The combined organic solutions were washed with water, brine, dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound as a white solid, 8.39g.

15 $^1\text{H NMR}$ (400 MHz, CDCl_3): δ [ppm] 1.41 (9H, s), 2.84 (2H, m), 3.61 (3H, s), 5.10 (1H, bs), 5.41 (1H, bs), 7.22-7.36 (5H, m).

20 LRMS: m/z 279.7 (MH^+)

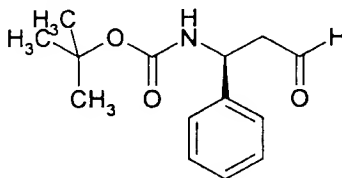
PREPARATION 6

Methyl (3S)-3-[(cyclobutylcarbonyl)amino]-3-phenylpropanoate



25 Obtained from the title compound of preparation 4 and cyclobutanecarbonyl chloride as a brown solid in 82% yield using a similar procedure to that in preparation 2.

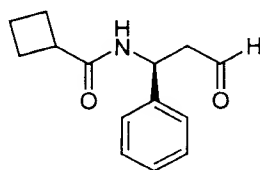
$^1\text{H-NMR}$ (300MHz, CDCl_3) : δ [ppm] 1.81-2.06 (2H, m), 2.10-2.40 (5H, m), 2.82-3.08 (2H, m), 3.62 (3H, s), 5.42 (1H, m), 6.42 (1H, d), 7.22-7.38 (5H, m).

PREPARATION 7*tert*-Butyl (1*S*)-3-oxo-1-phenylpropylcarbamate

5 Diisobutylaluminium hydride (1M in dichloromethane, 60ml, 60mmol) was cooled to -78°C and added dropwise to a solution of the title compound from preparation 5 (8.39g, 30mmol) in dichloromethane (150ml) at -78°C. The reaction was stirred for 90 minutes, then methanol (pre-cooled to -78°C) (40ml) was added. The mixture was allowed to warm to room temperature and poured into 2M hydrochloric acid (200ml). The layers were separated and
10 the aqueous phase extracted with dichloromethane (2x). The combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a white solid, 6.72g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.42 (9H, s), 2.86-3.00 (2H, m), 5.06 (1H, bs), 5.20 (1H, bs), 7.22-7.38 (5H, m), 9.75 (1H, s).

15 LRMS: m/z 250.1 (MH⁺).

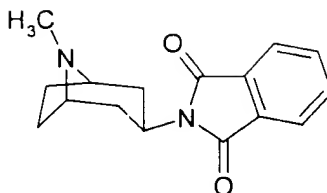
PREPARATION 8*N*-[(1*S*)-3-Oxo-1-phenylpropyl]cyclobutanecarboxamide

20 Obtained from the title compound of preparation 6 as a brown oil in 82% yield using a similar procedure to that in preparation 7.

¹H-NMR (300MHz, CDCl₃) : δ [ppm] 1.81-2.35 (6H, m), 2.90-3.10 (3H, m), 5.53 (1H, m), 5.98 (1H, bd), 7.23-7.39 (5H, m), 9.78 (1H, m).

25

PREPARATION 9*exo* 2-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-isoindole-1,3(2*H*)-dione



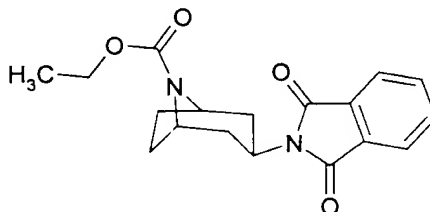
Diethyl azodicarboxylate (61.36ml, 0.39mol) was added dropwise over a period of 1 hour to a mixture of triphenylphosphine (102.2g, 0.39mol), phthalimide (52.04g, 0.35mol) and tropine (50g, 0.35mol) in tetrahydrofuran (400ml) at 0°C. The reaction mixture was stirred for 20 hours at room temperature, and the solvent evaporated under reduced pressure. The residue was dissolved in dichloromethane, the solution extracted with hydrochloric acid (2x1N) and the combined aqueous extracts basified with potassium carbonate. This aqueous solution was then extracted with dichloromethane (x3), the combined organic extracts dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was triturated with ether and filtered, to afford the title compound (12g). The filtrate was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (95:5 to 90:10) to afford additional title compound (30g total).

¹H-NMR (400MHz, CDCl₃) : δ [ppm] 1.40 (2H, m), 1.74 (2H, m), 2.12 (2H, m), 2.54 (3H, s), 2.63 (2H, m), 3.32 (2H, m), 4.52 (1H, m), 7.68 (2H, m), 7.80 (2H, m).

LRMS : m/z 271 (MH⁺)

PREPARATION 10

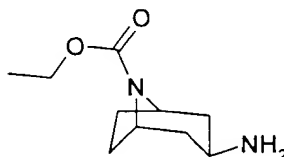
Ethyl exo 3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-8-azabicyclo[3.2.1]octane-8-
carboxylate



Ethyl chloroformate (22ml, 0.2mol) was added to a solution of the title compound from preparation 9 (20g, 7.4mmol) in toluene (200ml). The solution was heated to 90°C for 6 hours, then the mixture was cooled, and the solvent evaporated under reduced pressure to afford the title compound as a solid, 22.3g.

¹H-NMR (400MHz, CDCl₃) : δ [ppm] 1.33 (3H, t), 1.62 (2H, m), 1.85 (2H, m), 2.06 (2H, m), 2.61 (2H, t), 4.21 (2H, m), 4.38 (2H, m), 4.68 (1H, m), 7.68 (2H, m), 7.80 (2H, m).

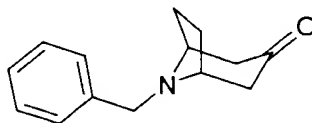
PREPARATION 11

Ethyl exo-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate

Hydrazine hydrate (3.73g, 74.6mmol) was added to a solution of the title compound of preparation 10 (22.4g, 68.2mmol) in ethanol (200ml) and the reaction was heated under reflux for 1½ hours. Water (500ml) was added to the cooled mixture, this solution acidified using concentrated hydrochloric acid (100ml), the precipitate was filtered off and the aqueous filtrate basified to pH 8 using sodium carbonate. This aqueous solution was extracted with dichloromethane (x3), the combined organic extracts dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a yellow oil, 12.7g.

¹H-NMR (300MHz, CDCl₃) : δ [ppm] 1.24 (3H, t), 1.40-1.60 (2H, m), 1.64 (2H, m), 1.85 (2H, m), 1.99 (2H, m), 2.41 (2H, bs), 3.20 (1H, m), 4.12 (2H, q), 4.28 (2H, bs).

LRMS : m/z 199 (MH⁺)

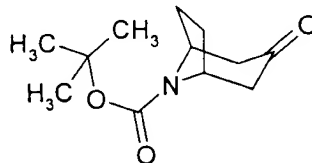
PREPARATION 128-Benzyl-8-azabicyclo[3.2.1]octan-3-one

A solution of 2,5 dimethoxytetrahydrofuran (50g, 378mmol) in 0.025M hydrochloric acid (160ml) was cooled to 0°C for 16 hours. Benzylamine hydrochloride (65g, 453mmol), ketomalonic acid (55g, 377mmol) and an aqueous solution of sodium acetate (300ml, 0.69M) were added and the reaction stirred at room temperature for 1 hour. The mixture was heated to 50°C for a further 90 minutes and then cooled in an ice bath whilst basifying to pH12 with 2N sodium hydroxide solution. The layers were separated, and the aqueous phase extracted with ethyl acetate (3x). The combined organic solutions were washed with water, dried (MgSO₄), filtered and evaporated under reduced pressure. The residual brown oil was distilled under reduced pressure (126°C @ 3mm of Hg) to afford the title compound as an off-white solid, 37.81g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.64 (2H, m), 2.06-2.14 (2H, m), 2.18 (1H, s), 2.23 (1H, s), 2.68 (1H, m), 2.72 (1H, m), 3.48 (2H, s), 3.73 (2H, s), 7.20-7.29 (1H, m), 7.32 (2H, m), 7.42 (2H, d).

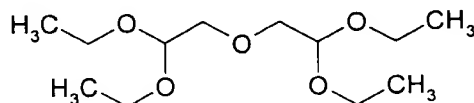
LRMS: m/z 216.3 (MH⁺).

PREPARATION 13

tert-Butyl 3-oxo-8-azabicyclo[3.2.1]octan-8-carboxylate

A mixture of the title compound from preparation 12 (15.0g, 69.7mmol) di-*tert*-butyl dicarbonate (18.2g, 83.4 mmol) and 20% w/w palladium hydroxide on carbon (3.0g) in ethyl acetate (165ml) was stirred for 4 hours at room temperature under a 39psi atmosphere of hydrogen. The mixture was filtered through Arbocel® and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of hexane:ether (100:0 to 50:50) to afford the title compound as a colourless oil which crystallized on standing, 16.2g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.48 (9H, s), 1.60-1.68 (2H, m), 2.00-2.11 (2H, m), 2.26-2.34 (2H, m), 2.48-2.82 (2H, m), 4.35-4.58 (2H, m).

PREPARATION 142-(2,2-Diethoxyethoxy)-1,1-diethoxyethane

15

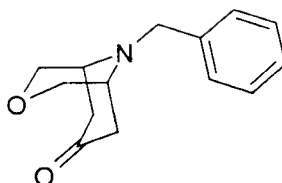
Glycolaldehyde diethyl acetal (45.4g, 338mmol) was added dropwise to a stirred solution of sodium hydride (14.3g, 60% dispersion in mineral oil, 357mmol) in xylene (100ml), and the reaction heated under reflux for 1 hour. The reaction mixture was cooled to room temperature and bromoacetaldehyde diethyl acetal (100g, 507mmol) was added. The resulting solution was heated under reflux for 20 hours, then cooled to room temperature. The solvent was removed under reduced pressure, and the residual solution was distilled under reduced pressure (80 °C @ 6mm Hg), to afford the title compound as a colourless oil, 60.8 g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.22 (12H, t), 3.55 (8H, m), 3.70 (4H, m), 4.60 (2H, t).

LRMS: m/z 269 (MNH₄⁺).

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PREPARATION 159-Benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one



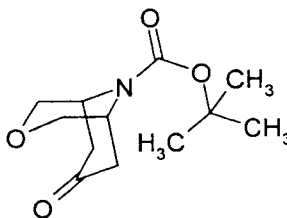
A solution of the title compound from preparation 14 (53.6g, 214mmol) in 0.025M hydrochloric acid (90ml) was stirred at room temperature for 16 hours. Benzylamine hydrochloride (30.7g, 213mmol), ketomalonic acid (26g, 178mmol), and a solution of sodium acetate (8g, 97mmol) in water (180ml) were added and the reaction was stirred at room temperature for 1 hour, then heated to 50 °C for 3 hours. The reaction mixture was cooled in an ice bath whilst basifying to pH12 using 1N sodium hydroxide solution. The layers were separated, and the aqueous phase extracted with ethyl acetate (2x). The combined organic solutions were washed with water, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using ethyl acetate as eluant, to afford the title compound as a white solid, 41.5g.

¹H NMR (400 MHz, CD₃OD): δ [ppm] 0.75 (2H, d), 1.38 (2H, m), 1.70 (2H, d), 2.19 (2H, d), 2.30 (2H, d), 2.45 (2H, s), 5.78 (1H, m), 5.83 (2H, t), 5.95 (2H, d).

LRMS: m/z 232.1 (MH⁺).

PREPARATION 16

tert-Butyl 7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate

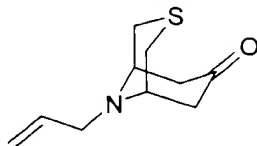


A mixture of the title compound from preparation 15 (10g, 43.2mmol), 20% palladium hydroxide on carbon (2g) and di-*tert*-butyl dicarbonate (11.32g, 51.8mmol) in ethyl acetate (100ml) was hydrogenated under 40psi of hydrogen for 16 hours at room temperature. The reaction was filtered through Arbocel® and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 94:6) to afford the title compound as a white solid, 9.80g.

¹H NMR (300MHz, CDCl₃): δ [ppm] 1.25 (2H, m), 1.50 (9H, s), 2.50 (2H, m), 3.50 (2H, m), 3.75 (2H, m), 4.38 (1H, m), 4.45 (1H, m).

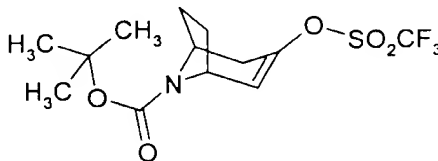
LRMS: m/z 264.0 (MNa⁺)

PREPARATION 17

9-Allyl-3-thia-9-azabicyclo[3.3.1]nonan-7-one

A solution of thiodiglycolaldehyde bis(diethyl acetal) (30g 112.3mmol) (Carbohydr. Res. 1981 90(2) 309) in 0.025M hydrochloric acid (90ml) was stirred at 100°C for 1 hour. The solution was cooled to room temperature and allylamine hydrochloride (13.65g, 146mmol), ketomalonic acid (16.4g, 112.7mmol) and sodium acetate (5.1g, 62mmol) in water (180ml) were added. The reaction was stirred at room temperature for 16 hours, then heated to 50 °C for 2 hours. The reaction was cooled in an ice bath whilst basifying to pH12 with 1N sodium hydroxide solution. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3X). The combined organic solutions were washed with water, dried (MgSO₄) filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluant of dichloromethane:methanol (99:1) to afford the title compound as a pink solid, 6.41g.

¹H NMR (400 MHz, CD₃Cl₃): δ [ppm] 2.15 (2H, d), 2.30 (2H, d), 2.55 (2H, m), 3.15 (2H, d), 3.30 (2H, d), 3.50 (2H, s), 5.20 (2H, m), 5.65 (1H, m).

PREPARATION 18tert-Butyl 3-[(trifluoromethyl)sulphonyloxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

Lithium diisopropylamine (2M in hexanes) (36ml, 71mmol) was added to a stirred solution of the title compound from preparation 13 (13.41g, 59mmol) in tetrahydrofuran at -78°C, and the reaction stirred for 2 hours. A solution of N-(5-chloro-2-pyridyl)triflimide (25.71g, 65.45mmol) in tetrahydrofuran (60ml) was added dropwise and the reaction was stirred for 2 hours at -78 °C then allowed to warm to room temperature. The solution was partitioned between dichloromethane and water, the layers separated and the organic phase was washed with brine, dried (MgSO₄) and evaporated under reduced pressure.

The residue was purified by column chromatography on basic activated aluminium oxide using an elution gradient of dichloromethane:methanol (100:0 to 98:2) to afford the title compound as a yellow oil, 14.1g.

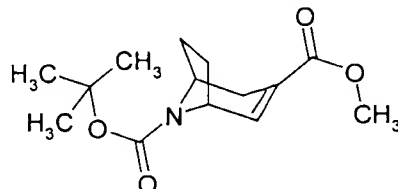
^1H NMR (400MHz, CDCl_3): δ [ppm] 1.50 (9H, s), 1.70 (1H, bs), 1.90-2.10 (3H, bm), 2.25 (1H, bs), 3.00 (1H, m), 4.40 (2H, m), 6.10 (1H, s).

LRMS: m/z 357 (MH^+)

5

PREPARATION 19

8-(*tert*-Butyl) 3-methyl 8-azabicyclo[3.2.1]oct-2-ene-3,8-dicarboxylate



A mixture of the title compound from preparation 18 (14.1g, 39.4mmol), palladium acetate (270mg), triphenylphosphine (620mg, 2.37mmol), triethylamine (11ml, 78.9mmol) and methanol (60ml) was stirred in *N,N*-dimethylformamide (150ml) at room temperature under a carbon monoxide atmosphere for 12 hours. The solution was partitioned between water and ethyl acetate, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic solutions were washed with water, then brine, dried (MgSO_4), filtered and evaporated under reduced pressure. The oily residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (100:0 to 95:5) to afford the title compound as a black oil, 10.4g.

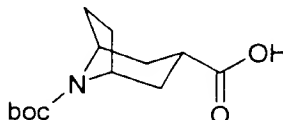
^1H NMR (400MHz, CDCl_3): δ [ppm] 1.45 (9H, s), 1.6 (1H, m), 1.95 (2H, m), 2.10 (1H, d), 2.15 (1H, m), 2.90 (1H, bm), 3.70 (3H, s), 4.30-4.50 (2H, bm), 7.10 (1H, s).

LRMS: m/z 535.2 (2MH^+)

20

PREPARATION 20

8-(*tert*-Butoxycarbonyl)-8-azabicyclo[3.2.1]octane-3-exo-carboxylic acid



A mixture of the title compound from preparation 19 (10.4g, 38.9mmol) and Raney® nickel (4g) in methanol (70ml) was stirred under 60psi of hydrogen for 7 hours at room temperature. The reaction was filtered through Celite® and the solvent removed under reduced pressure. The white solid obtained was stirred with sodium hydroxide (1.32g, 33mmol), water (10ml) and tetrahydrofuran (70ml) for 20 hours at room temperature. The reaction mixture was partitioned between water and dichloromethane, the layers separated and the aqueous phase was extracted with dichloromethane (2X). The combined organic solutions were dried (MgSO_4), filtered and evaporated under reduced pressure.

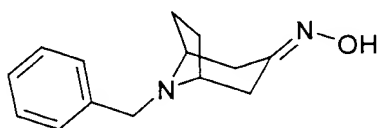
The residue was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol (98:2) to afford the title compound as a colourless oil, 3.23g

^1H NMR (400MHz, CDCl_3): δ [ppm] : 1.45 (9H, s), 1.65 (2H, m), 1.59 (2H, m), 1.90 (2H, m), 2.00 (2H, m), 2.82 (1H, m), 4.25 (2H, bd).

5 LRMS: m/z 279.0 (MNa^+).

PREPARATION 21

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one oxime



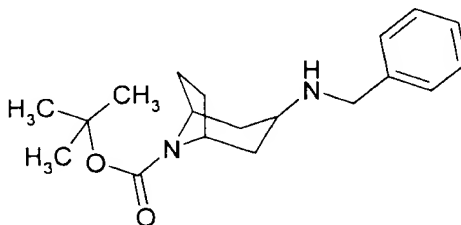
10 A mixture of the title compound from preparation 12 (17.72g, 82mmol), hydroxylamine hydrochloride (5.72g, 82mmol) and pyridine (7.2ml, 89mmol), were heated under reflux in ethanol (500ml) for 20 hours. The reaction was allowed to cool to room temperature and diluted with saturated sodium carbonate solution. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was partitioned between dichloromethane and water, the layers separated and the aqueous layer extracted with dichloromethane (2x).
15 The combined organic extracts were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound as a pale brown solid, 18.10g.

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.45-1.56 (1H, m), 1.60-1.67 (1H, m), 1.96-2.07 (2H, bm), 2.12 (1H, m), 2.21 (1H, m), 2.57 (1H, m), 2.97 (1H, m), 3.32 (2H, m), 3.64 (2H, s), 7.06 (1H, s), 7.21-7.28 (1H, m), 7.32 (2H, m), 7.38 (2H, d).

LRMS: m/z 231.2 (MH^+)

PREPARATION 22

25 *tert*-Butyl 3-endo-(benzylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate



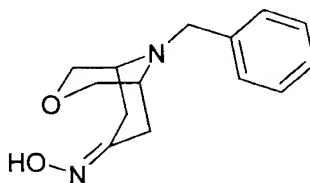
A solution of the title compound from preparation 13 (10.0g, 44.4mmol), benzylamine (4.85ml, 49.7mmol) and sodium triacetoxymethylborohydride (14.11g, 66.6mmol) was stirred for 16 hours at room temperature in a mixture of glacial acetic acid:dichloromethane (290ml) (1:9).
30 The solvents were evaporated under reduced pressure and the residue dissolved in ethyl

acetate, washed with saturated sodium carbonate solution and then water. The organic solution was dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an eluant of dichloromethane:methanol:0.88 ammonia (98:2:0.25) to afford the title compound as a white solid, 7.00g.

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.42-1.48 (11H, m), 1.52-1.61 (2H, m), 1.85-2.19 (5H, m), 2.95-3.03 (1H, m), 3.74 (2H, s), 4.03-4.23 (2H, m), 7.20-7.26 (1H, m), 7.26-7.32 (4H, m).

PREPARATION 23

9-Benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one oxime



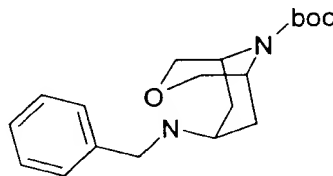
A solution of the title compound from preparation 15 (7g, 30mmol), hydroxylamine hydrochloride (2.31g, 33mmol) and pyridine (3ml, 37mmol) in ethanol (300ml) was heated under reflux for 2 hours. The reaction was allowed to cool to room temperature and saturated aqueous sodium carbonate solution added. The mixture was filtered and the solvent removed under reduced pressure. The residue was partitioned between water and dichloromethane and the layers separated. The aqueous phase was extracted with further dichloromethane (2x). The combined organic solutions were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound as a pale brown solid, 6.6g.

^1H NMR (400MHz, CDCl_3): δ [ppm] 2.25 (1H, s), 2.32 (1H, s), 2.40 (2H, m), 2.70 (2H, m), 2.90 (4H, bs), 3.12 (1H, s), 3.18 (1H, s), 3.70 (2H, d), 3.78 (2H, d), 7.25-7.40 (10H, m).

LRMS: m/z 247.1 (MH^+)

PREPARATION 24

tert-Butyl 7-endo-(benzylamino)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate



A mixture of the title compound from preparation 16 (9.80g, 40.6mmol), benzylamine (5.32ml, 48.7mmol), sodium triacetoxyborohydride (12.9g, 60.9mmol), and glacial acetic acid (2.5ml) in dichloromethane (120ml) was stirred at room temperature for 16 hours. The

reaction mixture was basified to pH 8 using saturated aqueous sodium carbonate solution. The layers were separated and the aqueous phase was extracted with dichloromethane (2x). The combined organic solutions were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as an oil, 2.45g.

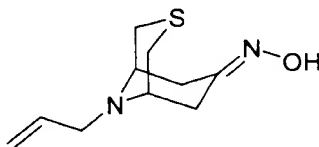
5 ¹H NMR (400MHz, CDCl₃): δ [ppm] 1.45 (9H, s), 1.75 (2H, d), 2.15 (2H, m), 2.72 (1H, m), 2.80 (1H, m), 3.58-3.72 (4H, m), 3.80 (2H, m), 3.95 (1H, d), 4.10 (1H, d), 7.18 (1H, m), 7.30 (4H, m).

LRMS: m/z 333.3 (MH⁺)

10

PREPARATION 25

9-Allyl-3-thia-9-azabicyclo[3.3.1]nonan-7-one oxime



The title compound from preparation 17 (6.4g, 32.4mmol), hydroxylamine hydrochloride (2.48g, 37.7mmol) and pyridine (3.2ml, 39mmol) were heated under reflux in ethanol (140ml) for 2 hours. The reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was partitioned between saturated sodium carbonate solution and dichloromethane the layers separated and the aqueous phase extracted with dichloromethane (2x). The combined organic solutions were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a brown solid, 6.33g.

20

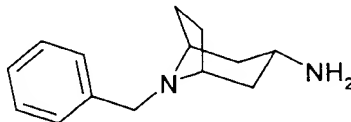
¹H NMR (400MHz, CDCl₃): δ [ppm] 2.15-2.45 (4H, m), 2.65 (1H, m), 3.1 (1H, d), 3.2-3.4 (6H, m), 5.1-5.3 (2H, m), 5.8 (1H, m), 8.0-8.6 (1H, bs).

LRMS: m/z 212.9 (MH⁺)

25

PREPARATION 26

8-Benzyl-8-azabicyclo[3.2.1]octan-3-exo-amine



A solution of the title compound from preparation 21 (18.10g, 79mmol) in pentanol (500ml) was heated under reflux with portionwise addition of sodium (22.0g, 957mmol) over 2 ½ hours. The reaction was then heated under reflux for a further 2 hours, then cooled to 0°C in an ice bath and water added until no more hydrogen gas evolved. The mixture was acidified using 6N hydrochloric acid and the phases separated. The organic layer was

30

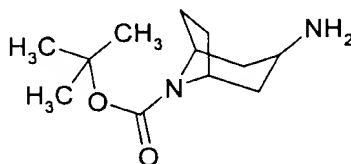
extracted with 6N hydrochloric acid (3x), the combined aqueous extracts were basified to pH12 with sodium hydroxide pellets (400g) and the aqueous solution extracted with ethyl acetate (3x). The combined organic solutions were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound, 15.65g.

- 5 ¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.20-1.40 (2H, bm), 1.48 (2H, m), 1.58 (2H, d), 1.64-1.76 (2H, bm), 2.00 (2H, bm), 2.95 (1H, m), 3.19 (2H, bs), 3.57 (2H, s), 7.18-7.26 (1H, m), 7.30 (2H, m), 7.37 (2H, d).
LRMS: m/z 217.3 (MH⁺).

10

PREPARATION 27

tert-Butyl 3-endo-amino-8-azabicyclo[3.2.1]octane-8-carboxylate

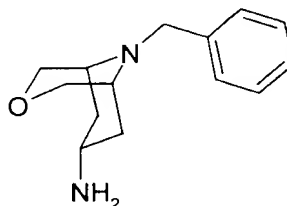


- A mixture of the title compound from preparation 22 (7.00g, 22.1mmol), ammonium formate (7.00g, 111mmol) and 20% w/w palladium hydroxide on carbon (700mg) in ethanol (200ml) was heated to 50°C, until gas evolution ceased. The cooled mixture was filtered through Arbocel® and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.25 to 95:5:0.5) to afford the title compound as a colourless oil, 4.70g.

LRMS: m/z 227.2 (MH⁺)

PREPARATION 28

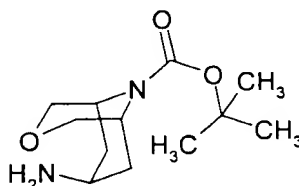
9-Benzyl-3-exo-oxa-9-azabicyclo[3.3.1]non-7-yl-amine



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The title compound was obtained (64%) from the title compound from preparation 23, using a similar procedure to that described in preparation 26.

¹H NMR (300 MHz, CDCl₃): δ [ppm] 1.70 (4H, m), 2.70 (2H, s), 3.70 (3H, m), 3.80-3.95 (6H, m), 7.20-7.40 (5H, m).

LRMS: m/z 233.1(MH⁺)PREPARATION 29tert-Butyl 7-endo-amino-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate

5

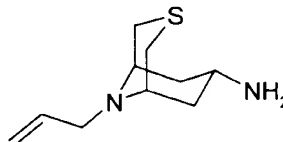
A mixture of the title compound from preparation 24 (2.45g, 7.7mmol) and 10% palladium on carbon (300mg) in ethyl acetate (40ml) was hydrogenated at 50psi for 36 hours at 50 °C. The cooled reaction was filtered through Arbocel® and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol: 0.88 ammonia (79:20:1) to afford the title compound as a colourless oil, 1.44g.

10

¹H NMR (400MHz, CDCl₃): δ [ppm] 1.45 (9H, s), 1.55 (2H, m), 2.18-2.30 (2H, m), 3.0 (1H, m), 3.60-3.78 (4H, m), 3.97 (1H, m), 4.10 (1H, m).

LRMS: m/z 242.5 (MH⁺)

15

PREPARATION 309-Allyl-3-thia-9-azabicyclo[3.3.1]non-7-yl-exo-amine

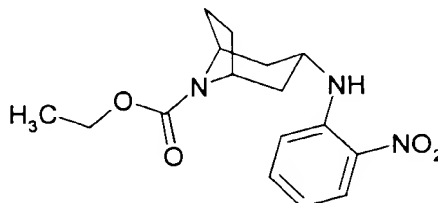
The title compound from preparation 25 (5.33g, 25.1mmol) was heated under reflux in pentanol (200ml) with portionwise addition of sodium (5.8g, 251.1mmol) over 1 hour. The reaction was then heated under reflux for a further 2 hours, then cooled to 0°C in an ice bath and water added until no more hydrogen gas evolved. The mixture was acidified with 6N hydrochloric acid, the layers separated and the organic phase extracted with 6N hydrochloric acid (3x). The combined aqueous extracts were basified to pH12 using sodium hydroxide pellets and the solution extracted with dichloromethane (2x). The combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure and freeze-dried from water/acetonitrile to afford the title compound as a brown powder, 4.73g.

25

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.30-1.70 (4H, m), 1.90 (2H, m), 2.10 (2H, d), 3.06-4.42 (6H, m), 4.62 (1H, m), 5.0-5.23 (2H, m), 5.80 (1H, m).

30

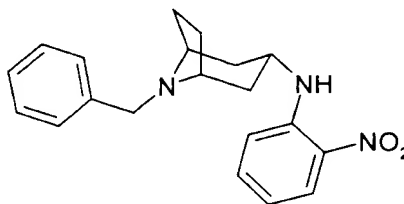
LRMS: m/z 199.1 (MH⁺)

PREPARATION 31Ethyl *exo* 3-(2-nitroanilino)-8-azabicyclo[3.2.1]octane-8-carboxylate

A mixture of the title compound from preparation 11 (12.7g, 64.1mmol), potassium carbonate (9.0g, 65.1mmol) and 1-fluoro-2-nitrobenzene (7.44ml, 70.5mmol) in N,N-dimethylformamide (30ml) was heated at 150°C for 2 ½ hours. The cooled reaction was concentrated under reduced pressure and the residue partitioned between water and ethyl acetate. The phases were separated, the organic layer dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 98:2) to afford the title compound as a solid, 16.9g.

¹H-NMR (300MHz, CDCl₃) : δ [ppm] 1.32 (3H, t), 1.60-1.80 (4H, m), 2.13 (4H, m), 4.02 (1H, m), 4.19 (2H, q), 4.41 (2H, bs), 6.62 (1H, m), 6.86 (1H, d), 7.42 (1H, m), 7.90 (1H, d), 8.16 (1H, m).

LRMS : m/z 320 (MH⁺)

PREPARATION 32N-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-*exo*-N-(2-nitrophenyl)amine

The title compound from preparation 26 (8.47g, 39mmol), 1-fluoro-2-nitrobenzene (4.55ml, 43mmol) and potassium carbonate (5.50g, 40mmol) were heated to 120°C in N,N-dimethylformamide for 4 ½ hours. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. The residue was taken up in ethyl acetate and washed with water. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol: 0.88 ammonia (98:2:0.25) to afford the title compound as a bright orange/yellow solid, 8.80g.

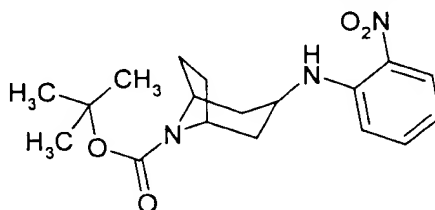
^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.66-1.80 (4H, m), 1.92-2.02 (2H, m), 2.08-2.20 (2H, m), 3.32 (2H, s), 3.60 (2H, s), 3.85 (1H, m), 6.60 (1H, m), 6.87 (1H, d), 7.20-7.28 (1H, m), 7.32 (2H, m), 7.38 (3H, m), 7.97 (1H, bd), 8.16 (1H, d).

LRMS: m/z 338.5 (MH^+).

5

PREPARATION 33

tert-Butyl 3-endo-(2-nitroanilino)-8-azabicyclo[3.2.1]octane-8-carboxylate



A mixture of the title compound from preparation 27 (4.69g, 20.7mmol), 1-fluoro-2-nitrobenzene (3.21g, 22.7mmol) and potassium carbonate (3.21g, 23.3mmol) were heated for 2 hours in *N,N*-dimethylformamide (75ml) at 100°C. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The layers were separated and the aqueous phase extracted with ethyl acetate. The organic solutions were dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound as a bright orange oil, which crystallized on standing, 7.50g.

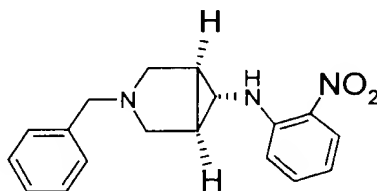
15

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.48 (9H, s), 1.80-1.87 (2H, m), 2.00-2.16 (4H, m), 2.16-2.41 (2H, m), 3.87-3.94 (1H, m), 4.14-4.39 (2H, m), 6.60-6.74 (1H, m), 6.69-6.74 (1H, d), 7.39-7.45 (1H, m), 8.16-8.21 (1H, d), 8.68-8.77 (1H, m).

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PREPARATION 34

N-[(1*R*,5*S*)-3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl]-*N*-(2-nitrophenyl)amine



Potassium carbonate (4.59g, 33.2mmol), followed by 1-fluoro-2-nitrobenzene (1.87g, 13.3mmol) were added to a solution of (1*R*,5*S*)-3-benzyl-3-azabicyclo[3.1.0]hex-6-ylamine (WO 9318001), (2.50g, 13.3mmol) in *N,N*-dimethylformamide (40ml), and the reaction mixture stirred at 130°C for 18 hours. The cooled mixture was filtered, and the filtrate concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, the phases separated, and the aqueous layer extracted with ethyl acetate (3x). The combined organic solutions were washed with brine, dried (MgSO_4), filtered and evaporated under

25

reduced pressure. The residual brown oil was purified by column chromatography on silica gel using an elution gradient of pentane:ethyl acetate (95:5 to 90:10) to afford the title compound as an orange crystalline foam, 3.11g.

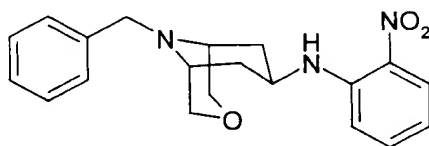
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.64 (2H, s), 2.54 (2H, m), 2.96 (1H, s), 3.18 (2H, m), 3.62 (2H, s), 6.68 (1H, m), 7.19 (1H, m), 7.29 (5H, m), 7.43 (1H, m), 7.96 (1H, bs), 8.16 (1H, m).

LRMS: m/z 309.8 (M⁺)

PREPARATION 35

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N-(9-Benzyl-3-oxa-9-azabicyclo[3.3.1]non-7-yl)-N-(2-nitrophenyl)-exo-amine



The title compound was obtained (63%) as a bright orange/yellow solid, from the compound of preparation 28, following the procedure described in preparation 32.

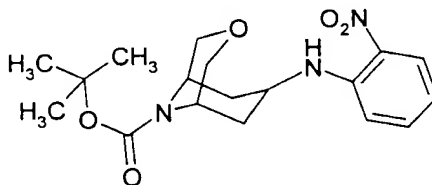
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.90-2.10 (4H, m), 1.90 (2H, s), 3.82 (2H, d), 3.90 (2H, s), 3.97 (2H, d), 4.90 (1H, m), 6.60 (1H, m), 7.00 (1H, d), 7.30 (1H, m), 7.35 (2H, m), 7.40 (3H, m), 8.00 (1H, d), 8.18 (1H, d).

LRMS: m/z 354.1 (MH⁺)

PREPARATION 36

20

tert-Butyl 7-endo-(2-nitroanilino)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate



The title compound was obtained as a yellow orange oil (99%), from the title compound of preparation 29, and 1-fluoro-2-nitrobenzene, following the procedure described in preparation 32.

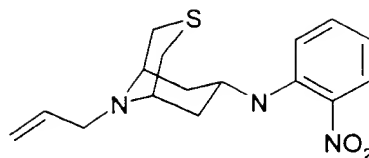
¹H NMR (400MHz, CDCl₃): δ [ppm] 1.50 (9H, s), 1.80 (2H, m), 2.38 (2H, m), 3.75 (2H, m), 3.85 (2H, m), 3.95 (1H, m), 4.10 (1H, m), 4.18 (1H, m), 6.60 (1H, m), 6.80 (1H, d), 7.40 (1H, m), 8.18 (1H, d), 9.22 (1H, d).

LRMS: m/z 364.1 (MH⁺)

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PREPARATION 37

N-(9-Allyl -3-thia-9-azabicyclo[3.3.1]non-7-yl)-N-(2-nitrophenyl)-exo-amine



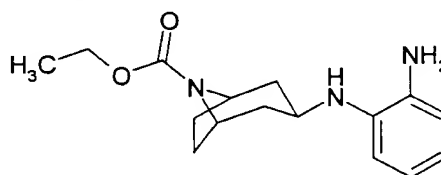
The title compound was obtained as a yellow orange oil (53%), from the title compound of preparation 30, and 1-fluoro-2-nitrobenzene, following the procedure described in preparation 32.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.90 (2H, m), 2.10-2.32 (4H, m), 3.25 (2H, s), 3.40 (4H, m), 5.11-5.3 (2H, m), 5.80 (2H, m), 6.62 (1H, m), 7.0 (1H, d), 7.40 (1H, m), 7.91 (1H, d), 8.15 (1H, d).

LRMS: m/z 320.3 (MH⁺)

PREPARATION 38

Ethyl 3-exo-(2-aminoanilino)-8-azabicyclo[3.2.1]octane-8-carboxylate



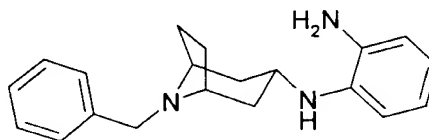
A mixture of the title compound from preparation 31 (16.9g, 52.9mmol), and 10% palladium on charcoal (2.0g) in methanol (50ml) and ethyl acetate (300ml), was hydrogenated at 1 atm of hydrogen, and room temperature for 15 hours. The reaction was filtered through Arbocel®, and the filtrate evaporated under reduced pressure to afford the title compound as a dark solid, 14.7g.

¹H-NMR (300MHz, CDCl₃) : δ [ppm] 1.30 (3H, t), 1.43-1.63 (2H, m), 1.79 (2H, m), 2.00-2.18 (4H, m), 3.18-3.35 (2H, bs), 3.78 (1H, m), 4.15 (2H, q), 4.39 (2H, bs), 6.65-6.80 (4H, m).

LRMS : m/z 290 (MH⁺)

PREPARATION 39

N¹-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-exo-1,2-benzenediamine



A mixture of the title compound from preparation 32 (8.80g, 26mmol) and 10% palladium on carbon (1.0g) in ethyl acetate (300ml) and methanol (50ml) was stirred under 1 atmosphere of hydrogen for 3 hours at room temperature. The reaction mixture was filtered

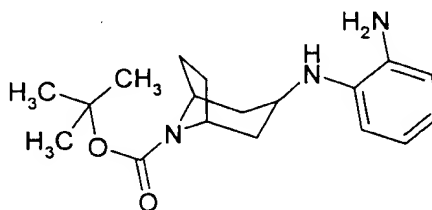
through Arbocel® and the filtrate removed under reduced pressure to afford the title compound as a dark brown oil, 7.23g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.59 (2H, m), 1.67-1.76 (2H, m), 1.92-2.02 (2H, m), 2.06-2.15 (2H, m), 3.27 (3H, m), 3.52-3.67 (3H, m), 6.60-6.72 (3H, m), 6.78 (1H, m), 7.20-7.28 (1H, m), 7.32 (2H, m), 7.38 (2H, d).

LRMS: m/z 308.6 (MH⁺).

PREPARATION 40

N-endo-(2-Aminophenyl)-N-(8-azabicyclo[3.2.1]oct-3-yl)amine



10

Tin (II) chloride dihydrate (25.0g, 111mmol) was added in five equal portions of 5g to a solution of the title compound from preparation 33 (7.50g, 21.6mmol) in ethanol (200ml) over a period of 25 minutes and the mixture was heated under reflux for 2 hours. The cooled mixture was concentrated under reduced pressure and the residue treated with 6M sodium hydroxide solution until basic. Ethyl acetate was added, the mixture filtered through Celite®, and the layers separated. The organic phase was dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a colourless oil, 3.10g.

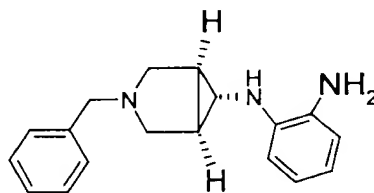
15

LRMS: m/z 218.3 (MH⁺)

20

PREPARATION 41

N-(2-Aminophenyl)-N-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)amine



25

Iron powder (2.44g, 43.6mmol) and calcium chloride (269mg, 2.42mmol) were added to a solution of the title compound from preparation 34 (1.50g, 4.85mmol), and the reaction heated under reflux for 18 hours. The cooled mixture was filtered through Celite®, washing through with ethanol, the filtrate evaporated under reduced pressure, and azeotroped with toluene. The residue was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (97.5:2.5:0.25) as eluant to afford the title compound as a dark brown oil, 751mg.

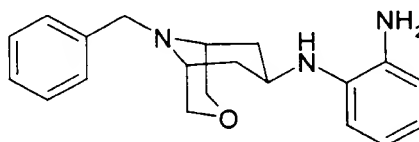
^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.58 (2H, m), 2.49 (2H, m), 2.81 (1H, s), 3.14 (2H, m), 3.48 (2H, s), 3.60 (2H, s), 6.68 (2H, m), 6.82 (1H, m), 6.95 (1H, m), 7.26 (5H, m).

LRMS: m/z 280.8 (MH^+)

5

PREPARATION 42

N^1 -(9-Benzyl-3-oxa-9-azabicyclo[3.3.1]non-7-yl)-1,2-exo-benzenediamine



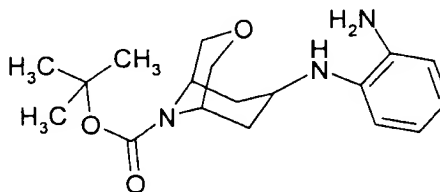
A mixture of the title compound from preparation 35 (4g, 11mmol) and 10% palladium on carbon (0.5g) in ethyl acetate (60ml) was hydrogenated under 1 atmosphere of hydrogen for 4 hours at room temperature. The reaction was filtered through Arbocel® and the solvent removed under reduced pressure to afford the title compound as a white solid, 2.87g.

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.80 (2H, m), 2.08 (2H, m), 2.78 (2H, s), 3.17 (1H, s), 3.30 (2H, s), 3.80 (2H, d), 3.90 (2H, s), 3.95 (2H, d), 4.60 (1H, m), 6.65 (1H, m), 6.70 (1H, m), 6.80 (2H, m), 7.25 (1H, m), 7.30 (2H, m), 7.40 (2H, d).

15 LRMS: m/z 323.7 & 325.3 (MH^+).

PREPARATION 43

tert-Butyl 7-endo-(2-aminoanilino)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate



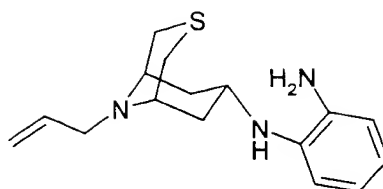
20 The title compound was obtained as a dark oil (97%) from the title compound from preparation 36, following the procedure described in preparation 42.

^1H NMR (400MHz, CDCl_3): δ [ppm] 1.00 (2H, bs), 1.50 (9H, s), 1.60 (1H, s), 1.85 (2H, d), 2.15-2.32 (2H, m), 3.70-3.85 (5H, m), 4.00 (1H, bs), 4.10 (1H, bs), 6.62 (2H, m), 6.70 (1H, m), 6.78 (1H, m).

25 LRMS: m/z 334.1 (MH^+)

PREPARATION 44

N^1 -(9-Allyl-3-thia-9-azabicyclo[3.3.1]non-7-yl)-1,2-exo-benzenediamine



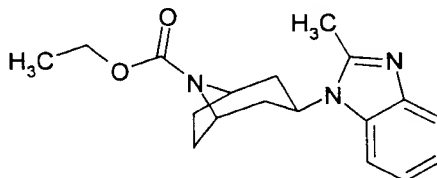
A mixture of the title compound from preparation 37 (3.9g 12.211mmol), iron powder (10g) and glacial acetic acid (10ml) was heated to reflux in water: ethanol (2:1 150ml) for 1 hour. The reaction was allowed to cool to room temperature, basified with 1M sodium hydroxide solution and diluted with ethyl acetate. The mixture was filtered, the layers separated and the aqueous phase extracted with ethyl acetate (3X). The combined organic solutions were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a brown oil, 3.7g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.77 (2H, m), 2.10-2.25 (4H, m), 2.45-3.20 (3H, bs), 3.20-3.45 (6H, m), 5.10-5.30 (2H, m), 5.40 (1H, m), 5.80 (1H, m), 6.60-6.85 (4H, m).

LRMS: m/z 290.1 (MH⁺)

PREPARATION 45

Ethyl 3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



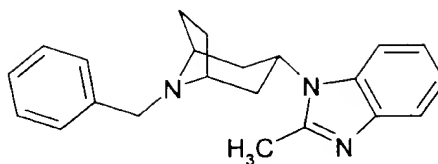
A solution of the the title compound from preparation 38 (14.7g, 50.8mmol) in triethylorthoacetate (200ml) was heated under reflux for 18 hours. The cooled reaction was evaporated under reduced pressure to afford the title compound as a brown oil, that crystallised on standing, 15.9g.

¹H-NMR (300MHz, CDCl₃) : δ [ppm] 1.19-1.31 (2H, m), 1.40 (3H, m), 1.82 (4H, m), 2.20 (2H, m), 2.62 (3H, s), 4.31 (2H, m), 4.57 (2H, bs), 4.74 (1H, m), 7.18 (2H, m), 7.49 (1H, m), 7.64 (1H, m).

LRMS : m/z 314 (MH⁺)

PREPARATION 46

1-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-exo-2-methyl-1H-benzimidazole



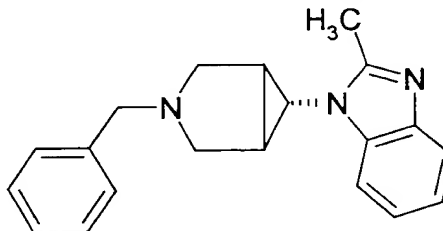
A mixture of the title compound from preparation 39 (17.00g, 55mmol) was heated under reflux in triethyl orthoacetate (250ml) for 16 hours, then cooled. Excess triethyl orthoacetate was evaporated under reduced pressure and the residue and 4-toluenesulphonic acid (3.00g) were heated under reflux in toluene (250ml) for 18 hours. The cooled mixture was evaporated under reduced pressure, the residue suspended in dichloromethane, and washed with saturated sodium carbonate solution, water and brine. The organic solution was dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound, 18.32g.

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.65-1.74 (2H, m), 1.74-1.82 (2H, m), 2.14-2.28 (2H, m), 2.58-2.72 (5H, m), 3.40 (2H, bs), 3.66 (2H, s), 4.56 (1H, m), 7.16-7.32 (3H, m), 7.37 (2H, m), 7.47 (2H, d), 7.66 (2H, m).

LRMS: m/z 331.9 (MH^+).

PREPARATION 47

1-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2-methyl-1H-benzimidazole



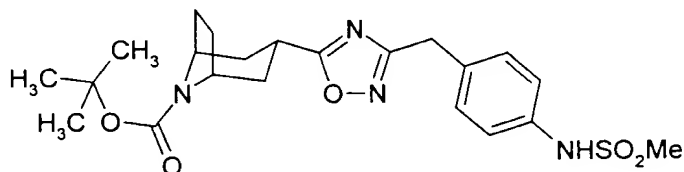
A solution of the title compound from preparation 41 (751mg, 2.69mmol) in acetic anhydride (10ml) was stirred at 130°C for 18 hours. The cooled solution was basified to pH 8 using saturated aqueous sodium bicarbonate solution, and this mixture extracted with ethyl acetate (3x). The combined organic extracts were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure. The residual brown oil was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (97.5:2.5:0.25) as eluant to afford the title compound as a brown oil, 200mg.

^1H NMR (300 MHz, CDCl_3): δ [ppm] 2.02 (2H, s), 2.60 (5H, m), 3.34 (2H, m), 3.59 (1H, s), 3.66 (2H, s), 7.18-7.43 (8H, m), 7.64 (1H, m).

LRMS: m/z 304.0 (MH^+).

PREPARATION 48

tert-Butyl 3-(3-exo-{4-[(methylsulphonyl)amino]benzyl}-1,2,4-oxadiazol-5-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate



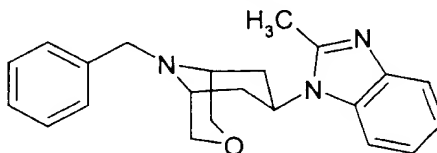
5 A solution of the title compound from preparation 20 (1.0g, 3.91mmol) in dichloromethane (10ml) was treated with N-ethyldiisopropylamine (815 μ l, 4.69mmol). Bis(tetramethylene)fluoroformamidinium hexafluorophosphate (1.48g, 4.68mmol) was added and the solution stirred at room temperature for 1 hour. N-Hydroxy-2-{4-
10 [(methylsulphonyl)amino]phenyl}ethanimidic acid (J.Med.Chem. 1993; 36(11); 1529), (1.14g, 4.69mmol) and N-ethyldiisopropylamine (680 μ l, 3.91mmol) were added, the resulting solution was stirred at room temperature for 48 hours, then heated to 50°C to concentrate the solution. Dioxan (20ml) was added, the solution was heated to 120°C for 3 hours, cooled to room temperature, diluted with ethyl acetate and basified with 10% aqueous sodium bicarbonate solution. The layers were separated, the aqueous phase extracted with ethyl acetate, and the
15 combined organic solutions were dried (MgSO₄), filtered and evaporated under reduced pressure.

The residue was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol (98:2) to afford the title compound as an oil, 1.48g

¹H NMR (400MHz, CDCl₃): δ [ppm] 1.45 (9H, s), 1.65 (3H, m), 1.75 (3H, m), 1.95-2.10
20 (6H, m), 3.65 (2H, s), 4.00 (2H, s), 6.90 (1H, bs), 7.20 (2H, d), 7.30(2H, m).

PREPARATION 49

9-Benzyl-7-(2-methyl-exo-1H-benzimidazol-1-yl)-3-oxa-7-azabicyclo[3.3.1]nonane



25 A mixture of the title compound from preparation 42 (2.87g, 8.9mmol) in triethyl orthoacetate (20ml) was heated under reflux for 8 hours. The cooled reaction mixture was evaporated under reduced pressure. The oily residue was purified by column chromatography on silica gel, using ethyl acetate:pentane (20: 80) as eluant to afford the title compound as a yellow oil, 1.47g.

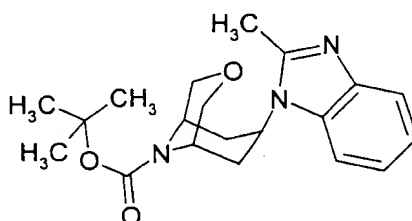
^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.78 (2H, m), 1.90 (3H, s), 2.05 (2H, m), 2.75 (2H, s), 3.80 (2H, d), 3.90 (2H, s), 3.95 (2H, d), 4.60 (1H, m), 6.60 (2H, m), 6.80 (1H, d), 6.90 (1H, m), 7.23 (1H, m), 7.30 (2H, m), 7.38 (2H, m).

LRMS: m/z 348.1 (MH^+)

5

PREPARATION 50

tert-Butyl 7-(2-methyl-*endo*-1*H*-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate



10 A solution of the title compound from preparation 43 (1.88g, 5.6mmol) in triethyl orthoacetate (20ml) was heated under reflux for 7 hours. The cooled mixture was concentrated under reduced pressure and the residue redissolved in toluene (250ml). 4-Toluenesulphonic acid (300mg, 1.57mmol) was added and the reaction heated under reflux for 2 hours, then cooled. The solvent was evaporated under reduced pressure, the residue
15 suspended in ethyl acetate, and washed with 10% aqueous sodium bicarbonate solution. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure to afford the title compound, 1.64g.

Found: C, 67.00; H, 7.67; N, 11.64%.

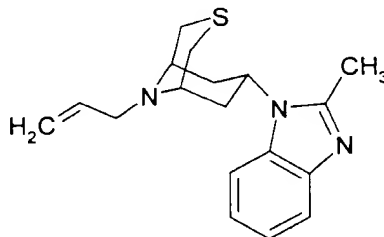
$\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_3$ requires C, 67.20; H, 7.67; N 11.64%.

20 ^1H NMR (400MHz, CDCl_3): δ [ppm] 1.30 (9H, s), 2.30 (2H, m), 2.55 (3H, s), 2.60 (2H, m), 3.62-3.80 (4H, m), 4.12 (1H, m), 4.25 (1H, d), 4.40 (1H, d), 7.20 (2H, m), 7.65 (2H, m).

LRMS: m/z 358.2 (MH^+)

PREPARATION 51

25 9-Allyl -7-(2-methyl-*exo*-1*H*-benzimidazol-1-yl)-3-thia-9-azabicyclo[3.3.1]nonane



A solution of the title compound from preparation 44 (3.68g, 12.21mmol) was heated under reflux in triethyl orthoacetate (20ml) for 16 hours. Excess triethyl orthoacetate was

evaporated under reduced pressure. The resulting oil was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol (99.5:1). The product was suspended in toluene (80ml) para-toluenesulfonic acid (catalytic) was added, and the mixture heated at reflux for 3 hours, then cooled and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium bicarbonate solution, water and brine. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a tan-coloured solid, 1.25g.

Found: C, 67.81; H, 7.44; N, 12.86%.

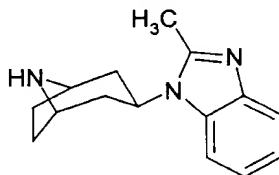
C₁₈H₂₃N₃S; 0.35H₂O requires C, 67.61; H, 7.47; N, 13.14%.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.50 (2H, m), 2.25 (2H, d), 2.63 (3H, s), 2.80-2.90 (2H, m), 3.30-3.60 (6H, m), 5.10-5.40 (2H, m), 5.85 (1H, m), 6.75 (1H, m), 7.20 (2H, m), 7.60 (1H, m), 7.71 (1H, m).

LRMS: m/z 314 (M+H⁺)

PREPARATION 52

exo 1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



A mixture of the title compound of preparation 45 (1.3g, 4.15mmol) in hydrochloric acid (6N, 30ml) was heated to 120°C for 20 hours. The cooled reaction mixture was basified with sodium hydroxide solution (15%) and the solution extracted with dichloromethane (x4). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as the eluant to afford the title compound as a solid, 620mg.

¹H-NMR (300MHz, CDCl₃) : δ [ppm] 1.64-1.98 (6H, m), 2.49 (2H, m), 2.59 (3H, s), 3.66 (2H, m), 4.50 (1H, m), 7.12 (2H, m), 7.51 (1H, m), 7.63 (1H, m).

LRMS : m/z 242 (MH⁺)

ALTERNATIVE METHOD

Ammonium formate (2.82g, 44.8mmol) was added the title compound from preparation 46 (2.84g, 8.6mmol) and palladium hydroxide (2.0g) in ethanol (60ml). The mixture was heated under reflux for 1 ½ hours and the reaction was allowed to cool to room temperature and filtered through Arbocel®. The solvent was evaporated under reduced

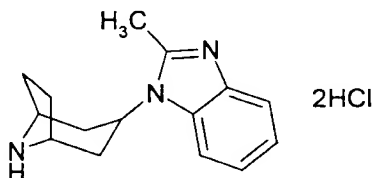
pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.25 to 95:5:0.5) to afford the title compound, 1.74g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.74-1.87 (4H, m), 1.90-2.02 (2H, m), 2.53 (2H, m), 2.63 (3H, s), 3.76 (2H, bm), 4.56 (1H, m), 7.13-7.25 (2H, m), 7.52-7.57 (1H, m), 7.64-7.71 (1H, m).

LRMS: m/z 242.1 (MH⁺).

PREPARATION 53

10 endo 1-(8-Azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride

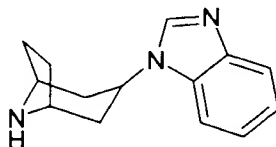


A solution of the title compound from preparation 40 (2.0g, 9.2mmol) and triethyl orthoacetate (50ml) were heated under reflux at 150 °C for 1 hour. The cooled mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate solution then water. The organic solution was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was dissolved in 50ml of 2.25M methanolic hydrochloric acid and heated under reflux for 24 hours. The solvent was removed under reduced pressure to afford the title compound as an off white solid, 1.05g.

¹H NMR (400 MHz, D₂O): δ[ppm] 2.20-2.42 (6H, m), 2.71-2.84 (2H, m), 2.80 (3H, s), 4.21-4.27 (2H, m), 4.94-5.06 (1H, m), 7.50-7.55 (2H, m), 7.68-7.74 (1H, m), 7.75 (1H, m).

PREPARATION 54

endo-1-(8-Azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole



25 A solution of the title compound from preparation 40 (1.10g, 5.06mmol) in 30ml of triethyl orthoformate was heated under reflux for 3 hours. The solvent was removed under reduced pressure and the residue was heated under reflux for 1 hour in 30ml of dioxan:concentrated hydrochloric acid (2:1). The solvents were removed under reduced pressure. The residue was basified with saturated sodium carbonate solution and extracted with dichloromethane (x3). The combined organic solutions were dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified using column chromatography

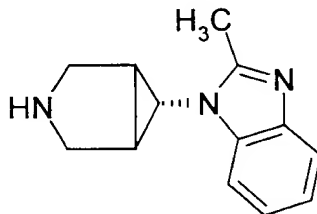
on silica gel using an eluant of dichloromethane:methanol:0.88 ammonia (98:2:0.25) to afford the title compound as a gum, 540mg.

LRMS: m/z 228 (MH⁺)

5

PREPARATION 55

1-(3-Azabicyclo[3.1.0]hex-6-yl)-2-methyl-1H-benzimidazole



A mixture of the title compound from preparation 47 (200mg, 0.70mmol), ammonium formate (1.4g, 22.2mmol), and 10% palladium on carbon (90mg) in methanol (10ml) was heated under reflux for 2 hours. The cooled reaction mixture was filtered through Celite®, washing through with additional methanol. The filtrate was evaporated under reduced pressure to give a yellow oil. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:1) as eluant to afford the title compound, 56mg.

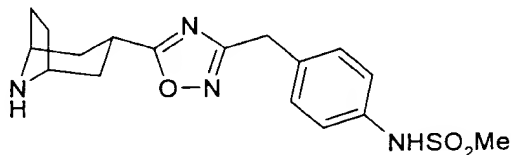
¹H NMR (400MHz, CDCl₃): δ [ppm] 2.12 (2H, m), 2.63 (4H, m), 3.02 (1H, m), 3.18 (2H, d), 3.50 (1H, s), 7.22 (2H, m), 7.42 (1H, m), 7.66 (1H, m).

LRMS: m/z 214.5 (MH⁺)

20

PREPARATION 56

N-(4-{[5-exo-(8-Azabicyclo[3.2.1]oct-3-yl)-1,2,4-oxadiazol-3-yl]methyl}phenyl)methanesulphonamide



A solution of the title compound from preparation 48 (1.48g, 3.20mmol) in 4M hydrochloric acid in dioxan (15ml) was stirred for 2 hours at room temperature. The solvent was evaporated under reduced pressure and the oily residue partitioned between dichloromethane and sodium carbonate solution. The phases were separated and the aqueous layer was extracted with dichloromethane (2x). The combined organic solutions were dried (MgSO₄), filtered and evaporated under reduced pressure.

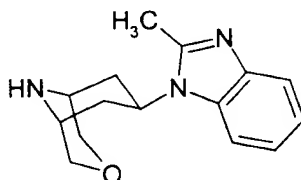
The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol: 0.88 ammonia (98:2:0 to 89:10:1) to afford the title compound as a brown solid, 375mg.

¹H NMR (400MHz, CDCl₃): δ [ppm] 1.70 (4H, m), 1.90 (6H, m), 3.00 (3H, s), 3.30 (1H, m), 3.58 (1H, bs), 3.62 (1H, m), 4.00 (2H, s), 7.15 (2H, d), 7.30 (2H, m).

LRMS: m/z 363.1 (MH⁺).

PREPARATION 57

7-(exo-2-Methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]nonane



10

Ammonium formate (1g, 15.8mmol) was added to the title compound of preparation 49 (1.12g, 3.2mmol) and palladium hydroxide (0.1g) in ethanol (50ml), and the mixture heated under reflux for 2 hours. The reaction was allowed to cool to room temperature and filtered through Arbocel®. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (97:3:0 to 89:5:1) to afford the title compound, 651mg.

15

Found: C, 67.86; H, 7.79; N, 15.47%.

C₁₅H₁₉N₂O; 0.5 H₂O requires C, 67.64; H, 7.57; N 15.78%.

20

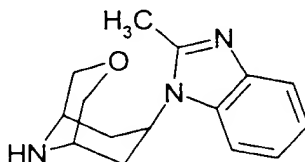
¹H NMR (400 MHz, CDCl₃): δ [ppm] 2.10 (2H, m), 2.65 (3H, s), 2.80 (2H, m), 3.18 (2H, s), 3.90-4.00 (4H, m), 5.07 (1H, m), 7.18 (2H, m), 7.60 (1H, d), 7.70 (1H, d).

LRMS: m/z 258.2 (MH⁺)

PREPARATION 58

7-endo-(2-Methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]nonane

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A solution of the title compound from preparation 50 (1.64g, 4.59mmol) and 4M hydrochloric acid in dioxan (15ml) was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue basified to pH 8 with saturated

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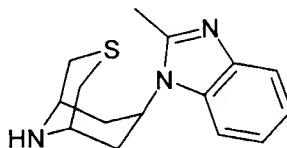
aqueous sodium carbonate solution. The aqueous layer was extracted with dichloromethane (2X). The combined organic solutions were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound as a dark solid, 1.08g.

^1H NMR (400MHz, CDCl_3): δ [ppm] 2.20 (2H, m), 2.60 (2H, m), 2.65 (3H, s), 3.25 (2H, m), 3.72 (4H, m), 4.70 (1H, m), 7.20 (2H, m), 7.70 (1H, m), 7.75 (1H, m).

LRMS: m/z 258.1 (MH^+)

PREPARATION 59

7-(exo-2-Methyl-1H-benzimidazol-1-yl)-3-thia-9-azabicyclo[3.3.1]nonane



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Tris(dibenzylideneacetone)dipalladium (176mg 0.192mmol) and 1,4 bis(diphenylphosphino)butane (82mg 0.192mmol) were stirred for 30 minutes in tetrahydrofuran. A solution of the title compound from preparation 51 (1.2g 3.80mmol) and 2-mercaptobenzoic acid (0.70g 4.6mmol) in tetrahydrofuran (10ml) was added and the solution stirred for 16 hours then evaporated under reduced pressure. The red solid was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol (97:3). The product was dissolved in dichloromethane and washed with saturated sodium bicarbonate solution, water and brine. The organic layer was dried (MgSO_4), filtered and evaporated under reduced pressure to afford the title compound as a tan solid, 0.66g

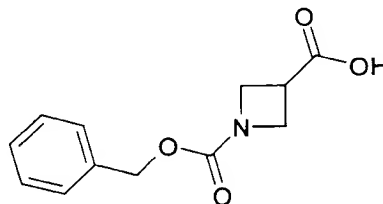
20

^1H NMR (400 MHz, CDCl_3): δ [ppm] 2.05 (2H, m), 2.52 (2H, d), 2.63 (3H, s), 2.83 (2H, m), 3.30 (2H, d), 3.60 (2H, s), 6.70 (1H, m), 7.1-7.23 (2H, m), 7.60 (1H, m), 7.70 (1H, m).

LRMS: m/z 274.3 (MH^+)

PREPARATION 60

1-[(Benzyloxy)carbonyl]-3-azetidinecarboxylic acid



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A solution of 3-azetidine carboxylic acid (0.50g, 4.9mmol), trimethylsilyl chloride (1.25ml, 9.8mmol) and N-ethyldiisopropylamine (2.20ml, 12.6mmol) was heated under reflux in dichloromethane (20ml) for 20 minutes. The reaction mixture was cooled in an ice bath and benzyl chloroformate (0.92ml, 6.4mmol) added. The mixture was stirred at room temperature

30

for 72 hours before quenching with saturated aqueous sodium bicarbonate solution. The layers were separated and the aqueous phase was acidified to pH2 with 2N hydrochloric acid and extracted with ethyl acetate (3x). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a brown oil,

5 1.01g.

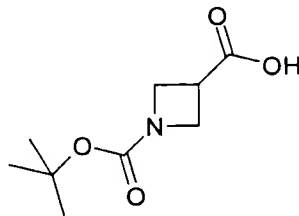
¹H NMR (400 MHz, CDCl₃): δ [ppm] 3.44 (1H, m), 4.21 (4H, d), 5.09 (2H, s), 7.28-7.41 (5H, m).

LRMS: m/z 253.1 (MNH₄⁺).

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PREPARATION 61

1-(*tert*-Butoxycarbonyl)-3-azetidinecarboxylic acid



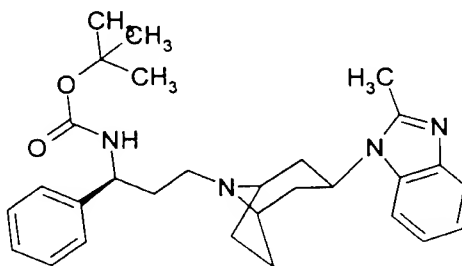
Di-*tert*-butyl dicarbonate (3.02g, 13.8mmol) was added to a suspension of 3-azetidine carboxylic acid (1g, 10mmol) and potassium carbonate (1.8g, 13mmol) in water (18ml) and dioxan (18ml) at 0°C, with stirring and allowed to warm to room temperature. The mixture was stirred for 15 hours and then concentrated under reduced pressure. The residue was acidified to pH 4 by addition of 1M citric acid solution and extracted with dichloromethane (x3). The combined organic extracts were washed with water then brine, dried (MgSO₄), filtered and solvent evaporated under reduced pressure to afford the title compound as a white solid, 2.1g.

20 ¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.44 (9H, s), 3.38 (1H, m), 4.14 (4H, m).

LRMS: m/z 200 (MH⁺).

PREPARATION 62

tert-Butyl (1S) 3-[*exo* 3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate



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Sodium triacetoxyborohydride (395mg, 1.86mmol) and glacial acetic acid (75mg, 1.25mmol) were added to a solution of the title compounds of preparations 52 (300mg,

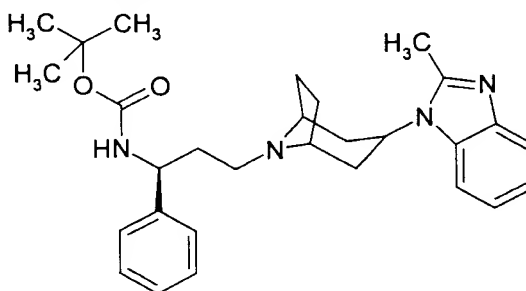
1.24mmol) and 7 (341mg, 1.37mmol) in dichloromethane (10ml), and the reaction stirred at room temperature for 18 hours. The mixture was basified with 10% aqueous sodium carbonate solution, and extracted with dichloromethane (2x). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a white foam, 444mg.

¹H-NMR (400MHz, CDCl₃) : δ [ppm] 1.37 (9H, s), 1.72 (4H, m), 1.88 (1H, m), 1.98-2.15 (3H, m), 2.50 (2H, t), 2.62 (5H, m), 3.39 (1H, m), 3.45 (1H, m), 4.55 (1H, m), 4.87 (1H, s), 6.50 (1H, m), 7.20 (2H, m), 7.25 (1H, m), 7.36 (4H, m), 7.58 (1H, m), 7.66 (1H, d).

LRMS : m/z 475 (MH⁺)

PREPARATION 63

tert-Butyl (1S) 3-[endo 3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate

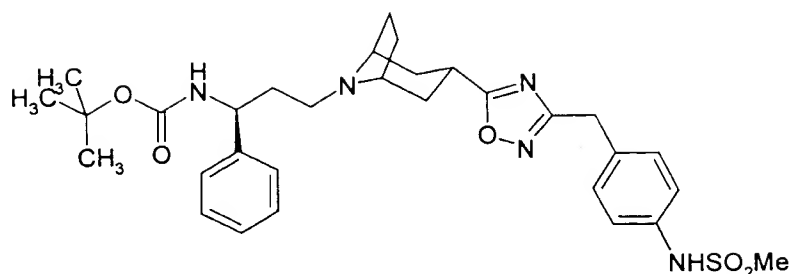


A solution of the title compounds from preparations 7 (480mg, 1.93mmol), and 53 (600mg, 1.91mmol) and sodium triacetoxymethylborohydride (600mg, 2.83mmol) were stirred together in a 30ml mixture of glacial acetic acid:dichloromethane (1:9) for 30 minutes at room temperature. The solvents were removed under reduced pressure and the residue basified with 6N NaOH then extracted with dichloromethane (x3). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a foam, 900mg.

LRMS : m/z 475.1 (MH⁺)

PREPARATION 64

tert-Butyl (1S)-3-[3-exo-(3-[4-[(methylsulphonyl)amino]benzyl]-1,2,4-oxadiazol-5-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate



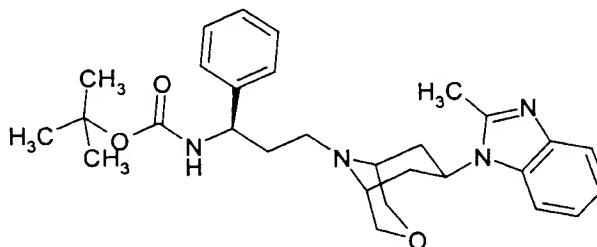
The title compound was prepared from the title compounds from preparations 7 and 56, following a similar procedure to that described in preparation 62.

The crude product was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (99:1 to 98:2) to afford the title compound as a white foam, 392mg.

^1H NMR (400MHz, CDCl_3): δ [ppm] 1.38 (9H, s), 1.55 (5H, bs), 1.70-2.10 (12H, m), 2.35 (3H, m), 3.00 (3H, s), 3.19 (1H, m), 3.25 (1H, m), 3.37 (1H, m), 4.00 (2H, s), 7.10-7.30 (9H, m).

PREPARATION 65

tert-Butyl (1*S*)-3-[7-(*exo*-2-methyl-1*H*-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropylcarbamate



The title compound was obtained as a white solid (90%), from the title compounds of preparations 7 and 57, following the procedure of preparation 64.

Found: C, 69.10; H, 7.91; N, 10.47%.

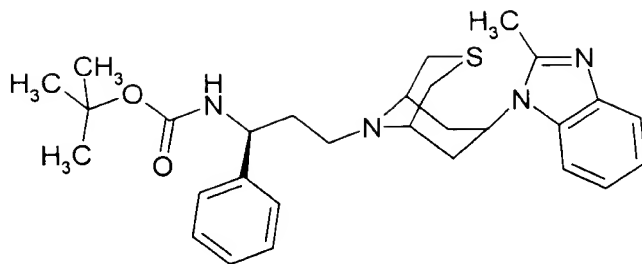
$\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_3$; 0.8 H_2O requires C, 68.97; H, 7.90; N 10.37%.

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.40 (9H, s), 1.78 (2H, m), 1.90-2.08 (2H, m), 2.62 (3H, s), 2.65-2.95 (6H, m), 3.92 (2H, m), 4.05 (2H, m), 4.90 (1H, s), 5.65 (1H, m), 6.15 (1H, d), 7.18 (2H, m), 7.25-7.38 (5H, m), 7.42 (1H, d), 7.70 (1H, d).

LRMS: m/z 491.2 (MH^+)

PREPARATION 66

tert-Butyl(1*S*)-3-[7-(*exo*-2-methyl-1*H*-benzimidazol-1-yl)-3-thia-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropylcarbamate



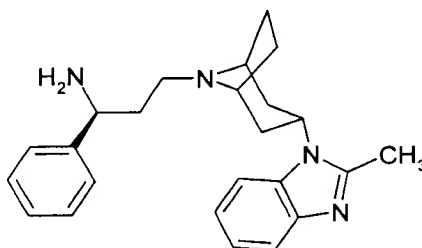
The title compound was obtained as a white solid (77%), from the title compounds of preparations 7 and 59, following the procedure of preparation 64.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.4 (9H, s), 1.80-2.0 (4H, m), 2.36 (2H, t), 2.64 (3H, s), 2.70-2.90 (4H, m), 3.35 (2H, s), 3.45 (2H, t), 4.90 (1H, br s), 6.0 (1H, br s), 6.75 (1H, m), 7.20 (2H, m), 7.25-7.40 (5H, m), 7.55 (1H, d), 7.70 (1H, d).

LRMS: m/z 507.1 (MH⁺)

PREPARATION 67

(1S) 3-[exo 3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylamine



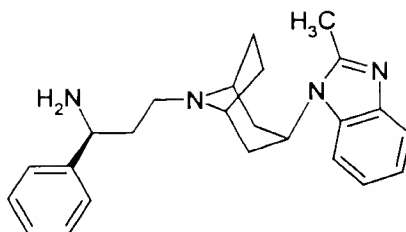
A solution of the title compound from preparation 62 (1.00g, 2.1mmol) and trifluoroacetic acid (8ml) in dichloromethane (20ml) was stirred for 60 hours at room temperature. The solvent was concentrated under reduced pressure and the residue quenched with aqueous saturated sodium carbonate solution. This aqueous mixture was extracted with dichloromethane (3x) and the combined organic extracts washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound, 600mg.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.60-1.84 (6H, m), 1.92 (2H, m), 2.01-2.14 (2H, bm), 2.51 (3H, m), 2.54-2.66 (4H, m), 3.44 (2H, m), 4.17 (1H, m), 4.52 (1H, m), 7.18 (2H, m), 7.22-7.28 (1H, m), 7.31-7.41 (4H, m), 7.47-7.53 (1H, m), 7.64-7.69 (1H, m).

LRMS: m/z 375.6 (MH⁺).

PREPARATION 68

(1S) 3-[endo 3-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylamine

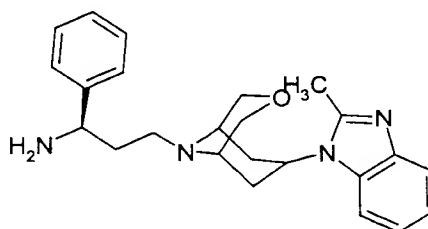


A solution of the title compound from preparation 63 (900mg, 1.90mmol) was stirred for 1 hour at 40°C in a 30ml mixture of dichloromethane:trifluoroacetic acid (4:1). The solvents were removed under reduced pressure, the residue basified with saturated sodium carbonate solution and extracted with dichloromethane (x3). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to afford the title compound as a foam, 330mg.

LRMS: m/z 375.2 (MH⁺)

PREPARATION 69

(1S)-3-[7-endo-(2-Methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenyl-1-propanamine



A mixture of the title compounds from preparations 58 (500mg, 1.94mmol), and 7 (533mg, 2.13mmol), sodium triacetoxymethylborohydride (618mg, 2.91mmol), and glacial acetic acid (115ml) in dichloromethane (10ml) was stirred at room temperature for 24 hours. The reaction was diluted with aqueous saturated sodium carbonate solution, and the phases separated. The aqueous layer was extracted with dichloromethane (2x) and the combined organic extracts washed with brine, dried (Na₂SO₄), filtered and evaporated under reduced pressure. The resulting brown foam was stirred in 4M hydrochloric acid in dioxan (20ml) for 1 hour. The excess of solvent was evaporated under reduced pressure and the residue was basified with aqueous saturated sodium carbonate solution. The aqueous layer was extracted with dichloromethane (3X). The combined organic solutions were washed with brine, dried (Na₂SO₄), filtered and evaporated under reduced pressure to afford the title compound as a brown solid, 729mg.

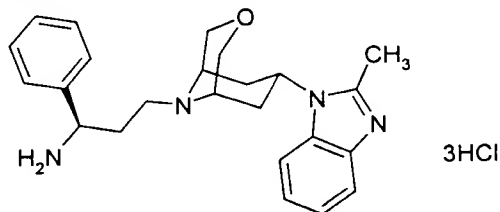
^1H NMR (400MHz, CDCl_3): δ [ppm] 1.90 (2H, m), 2.30 (2H, m), 2.60 (2H, m), 2.64 (3H, s), 2.80 (2H, m), 3.00 (2H, m), 3.40 (2H, d), 3.70 (2H, m), 3.90 (2H, m), 4.07 (1H, t), 4.80 (1H, m), 7.20 (2H, m), 7.25 (1H, m), 7.35 (4H, m), 7.68 (1H, m), 7.78 (1H, m).

LRMS: m/z 391.1 (MH^+)

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PREPARATION 70

(1S)-3-[7-(exo-2-Methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenyl-1-propanamine trihydrochloride



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A solution of the title compound from preparation 65 (1.10g, 2.24mmol) in 4M hydrochloric acid in dioxan (10ml) was stirred for 1 hour. The solvent was evaporated under reduced pressure to afford the title compound as a white solid, 1.30g.

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ [ppm] 2.45-2.70 (3H, m), 2.92 (3H, s), 3.40 (4H, m), 3.72 (1H, m), 3.83 (1H, m), 3.95-4.10 (2H, m), 4.30 (1H, d), 4.45 (2H, m), 5.82 (1H, m), 7.35-7.55 (5H, m), 7.60 (2H, d), 7.80 (1H, d), 8.80 (2H, bs), 9.10 (1H, d), 12.28 (1H, bs).

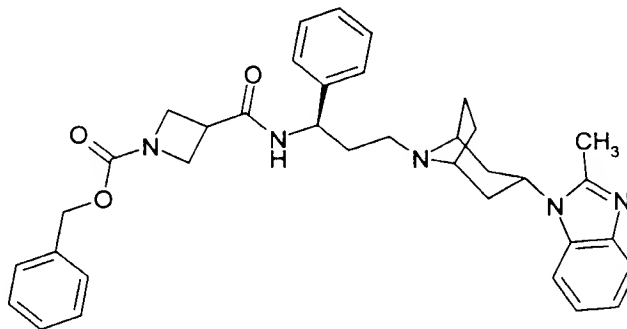
15

LRMS: m/z 391.2 (MH^+)

PREPARATION 71

Benzyl 3-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl] amino)carbonyl]-1-azetidine carboxylate

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A solution of the title compound from preparation 67 (222mg, 0.59mmol) in dichloromethane (5ml) was added to the title compound from preparation 60 (136mg, 0.58mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (136mg, 0.71mmol), N-ethyldiisopropylamine (108 μl , 0.62mmol) and 1-hydroxybenzotriazole hydrate (88mg, 0.65mmol) in dichloromethane (5ml). The reaction mixture was stirred at room

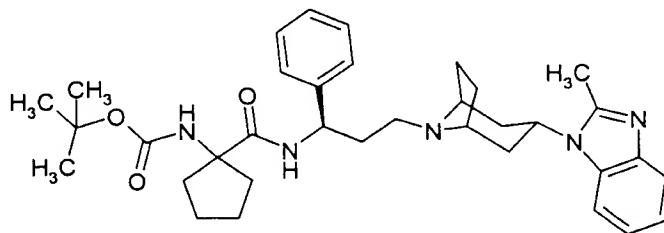
temperature for 20 hours. The solvent was evaporated under reduced pressure and the residue taken up in ethyl acetate, washed with water, brine, dried (MgSO₄) filtered and evaporated under reduced pressure. The residual pale brown solid was purified by column chromatography on silica gel, using an eluant of dichloromethane:methanol:0.88 ammonia (95:5:0.5) to afford the title compound as a white solid, 279mg.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.62-1.72 (2H, bm), 1.76 (2H, m), 1.94-2.18 (4H, m), 2.44-2.58 (3H, m), 2.58-2.68 (4H, m), 3.21-3.32 (1H, m), 3.44 (2H, m), 4.08-4.17 (2H, bm), 4.55 (1H, m), 5.08 (2H, s), 5.24 (1H, m), 7.08-7.24 (3H, m), 7.28-7.41 (9H, m), 7.46-7.54 (1H, m), 7.63-7.72 (1H, m).

LRMS: m/z 592.6 (MH⁺).

PREPARATION 72

tert-Butyl 1-[[[(1S)-3-exo-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]amino]carbonyl]cyclopentylcarbamate



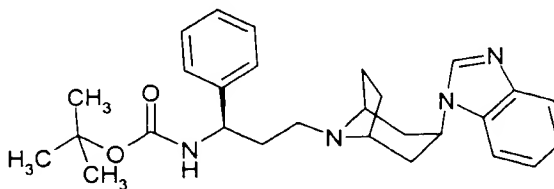
The title compound was obtained as a white solid (85%), from the title compound of preparation 67 and 1-[(*tert*-butoxycarbonyl)amino]cyclopentanecarboxylic acid (J. Med. Chem. 14; 1971; 904), (61mg, 0.27mmol), following the procedure described in preparation 71.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.42 (9H, s), 1.54-1.86 (10H, m), 1.90-2.20 (5H, m), 2.20-2.37 (2H, bm), 2.37-2.64 (7H, m), 3.41 (2H, bs), 4.52 (1H, m), 4.77 (1H, bm), 5.16 (1H, m), 7.14-7.22 (2H, m), 7.30-7.38 (4H, m), 7.42-7.58 (2H, bm), 7.63-7.71 (1H, m).

LRMS: m/z 586.1 (MH⁺).

PREPARATION 73

tert-Butyl (1S)-3-endo-[3-(1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate

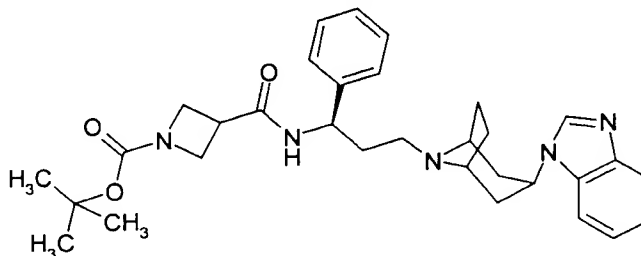


A mixture of the title compounds from preparations 7 (592mg, 2.37mmol), and 54 (540mg, 2.37mmol) and sodium triacetoxyborohydride (750mg, 3.54mmol) were stirred together in a 25ml mixture of glacial acetic acid:dichloromethane (1:9) for 30 minutes at room temperature. The solvents were removed under reduced pressure, the residue suspended in saturated sodium carbonate solution and extracted with dichloromethane (x3). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an eluant of dichloromethane:methanol:0.88 ammonia (98:2:0.25) to afford the title compound as a foam, 750mg.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.35-1.48 (9H, m), 1.60-1.71 (2H, m), 1.87-2.16 (6H, m), 2.29-2.37 (2H, m), 2.69-2.81 (2H, m), 3.32-3.39 (1H, m), 3.42-3.47 (1H, m), 3.68-3.76 (1H, m), 4.69-4.82 (1H, m), 4.82-4.95 (1H, m), 6.63-6.73 (1H, m), 7.23-7.39 (7H, m), 7.39-7.53 (1H, m), 7.77-7.82 (1H, m), 8.05 (1H, s)

PREPARATION 74

tert-Butyl 3-[(1S)-3-endo-[3-(1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]amino)carbonyl]-1-azetidinecarboxylate



A solution of the title compound from preparation 73 (750mg, 1.63mmol) was stirred for 5 hours at room temperature in a mixture of dichloromethane:trifluoroacetic acid (4:1), (20ml). The solvents were removed under reduced pressure, the residue was basified using saturated sodium hydrogen carbonate solution and extracted with dichloromethane (x3). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an eluant of dichloromethane:methanol:0.88 ammonia (98:2:0.25) to afford the title compound as a foam, 480mg.

A mixture of this intermediate amine (480mg, 1.33mmol), the title compound from preparation 61 (250mg, 1.33mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280mg, 1.46mmol) were stirred together for 1 hour at room temperature in dichloromethane (10ml). The solvent was removed under reduced pressure, the residue dissolved in ethyl acetate and washed with saturated sodium hydrogen carbonate solution and

water. The organic solution was dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an eluant of dichloromethane:methanol:0.88 ammonia (98:2:0.25) to afford the title compound as a foam, 730mg.

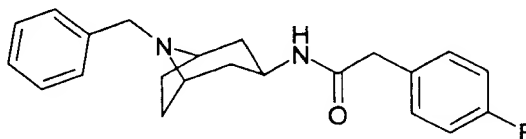
5 ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.42 (9H, s), 1.60-1.69 (2H, m), 1.96-2.10 (6H, m), 2.29-2.35 (2H, m), 2.55-2.74 (2H, m), 3.13-3.26 (1H, m), 3.34-3.40 (2H, m), 4.02-4.18 (4H, m), 4.66-4.76 (1H, m), 5.19-5.26 (1H, m), 7.00-7.13 (1H, bs), 7.23-7.32 (5H, m), 7.32-7.45 (3H, m), 7.77-7.82 (1H, m), 8.06 (1H, s).

LRMS: m/z 544.4 (MH^+)

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PREPARATION 75

N-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-3-exo-(4-fluorophenyl)propanamide



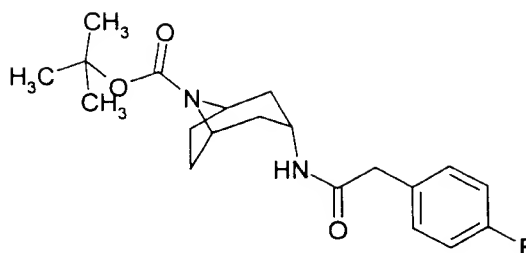
15 The title compound from preparation 26 (2.0g, 9.2mmol) was added to 4-fluorophenylacetic acid (1.42g, 9.2mmol) N-ethyl-diisopropylamine (1.6ml, 9.2mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.77g, 9.2mmol), and 1-hydroxybenzotriazole hydrate (1.41, 9.2mmol) in dichloromethane (20ml). The reaction mixture was stirred at room temperature for 16 hours then saturated aqueous sodium carbonate solution (30 ml) was added. The layers were separated and the aqueous phase
20 was extracted with dichloromethane (2x). The combined organic extracts were washed with water, dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol: 0.88 ammonia (98:2:0 to 95.5:4:0.5) to afford the title compound as a white solid, 1.04g.

25 ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.40 (2H, m), 1.70 (2H, d), 1.75 (2H, m), 2.02 (2H, m), 3.18 (2H, s), 3.50 (4H, s), 4.10 (1H, m), 7.00 (2H, m), 7.15-7.32 (7H, m).

LRMS: m/z 353.1 (MH^+).

PREPARATION 76

30 *tert*-Butyl 3-endo-{[2-(4-fluorophenyl)acetyl]amino}-8-azabicyclo[3.2.1]octane-8-carboxylate



The title compound was obtained (86%) as a white solid, from the title compound of preparation 27 and 4-fluorophenylacetic acid, following a similar procedure to that described in preparation 75.

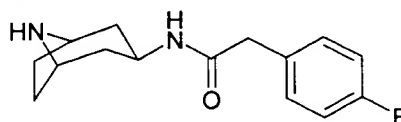
5 ^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.10-1.30 (2H, m), 1.38-1.60 (11H, m), 1.83 (2H, m), 2.0-2.30 (2H, bm), 3.56 (2H, s), 4.0-4.20 (3H, m), 5.70 (1H, m), 7.10 (1H, m), 7.20-7.30 (3H, m)

LRMS: m/z 385.3 (MNa^+).

10

PREPARATION 77

N-(8-Azabicyclo[3.2.1]oct-3-yl)-3-exo-(4-fluorophenyl)propanamide



A mixture of the title compound from preparation 75 (2.69g, 7.63mmol) and 10% palladium on carbon (0.5g) in ethyl acetate (30ml) was hydrogenated at 50psi at 50 °C for 48 hours. The reaction mixture was filtered through Arbocel® and the filtrate removed under reduced pressure to afford the title compound as a white solid, 1.96g.

15

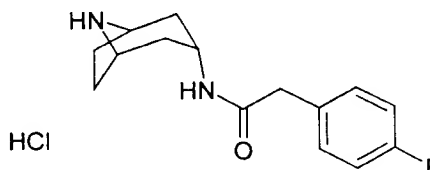
^1H NMR (300 MHz, CDCl_3): δ [ppm] 1.30 (2H, m), 1.65-1.80 (4H, m), 1.80-2.20 (5H, m), 3.55 (2H, s), 4.15 (1H, m), 5.20 (1H, d), 7.00 (2H, m), 7.20 (2H, m).

LRMS: m/z 263.1 (MH^+).

20

PREPARATION 78

N-(8-Azabicyclo[3.2.1]oct-3-yl)-3-endo-(4-fluorophenyl)propanamide hydrochloride



A solution of the title compound from preparation 76 (2.04g, 5.62mmol) was stirred in 4M hydrochloric acid solution in dioxan (20ml). The excess solvent was evaporated under reduced pressure to afford the title compound as a white solid, 1.55g.

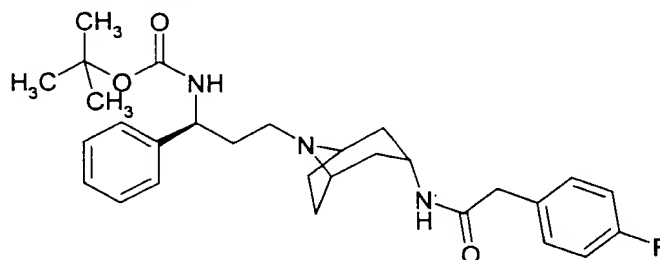
25

^1H NMR (400 MHz, DMSO- d_6): δ [ppm] 1.85 (4H, m), 2.1 (4H, m), 3.45 (2H, s), 3.7 (1H, m), 3.85 (2H, bs), 7.1 (2H, m), 7.25 (2H, m), 8.15 (1H, d), 8.85 (1H, bs), 9.1 (1H, bs).
LRMS: m/z 262.9 (MH^+).

5

PREPARATION 79

tert-Butyl (1*S*)-3-(3-*endo*-{[2-(4-fluorophenyl)acetyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropylcarbamate



The title compound was obtained as a white solid (68%), from the title compounds of preparations 7 and 78, following a similar procedure to that described in preparation 64.

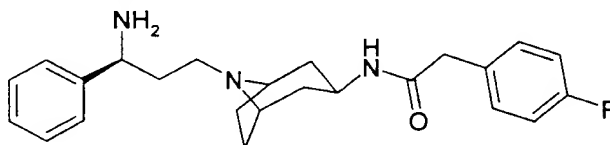
^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.0-2.0 (18H, m), 2.10-2.30 (4H, m), 3.02 (1H, s), 3.15 (1H, s), 3.50 (1H, s), 4.15 (1H, q), 4.77 (1H, bs), 5.53 (1H, d), 7.04 (2H, m), 7.2-7.4 (7H, m).

LRMS: m/z 496.9 (MH^+).

15

PREPARATION 80

N-(8-[(3*S*)-3-*exo*-Amino-3-phenylpropyl]-8-azabicyclo[3.2.1]oct-3-yl)-3-(4-fluorophenyl)propanamide hydrochloride



A mixture of the title compounds from preparations 77 (1.96g, 7.47mmol) and 7 (2.9g, 9.58mmol), sodium triacetoxyborohydride (2.37g, 11.2mmol), and glacial acetic acid (0.5ml) in dichloromethane (30ml) was stirred at room temperature for 16 hours. The reaction mixture was basified to pH 8 using saturated sodium bicarbonate solution. The phases were separated and the aqueous layer was extracted with dichloromethane (2x). The combined organic extracts were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 95:5) to afford 2.49g of a white solid.

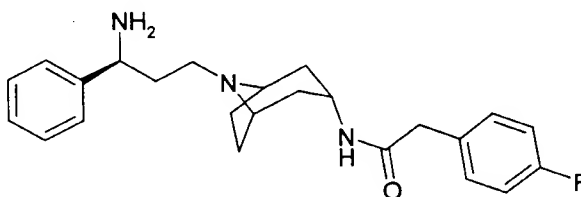
This intermediate was stirred in 4M hydrochloric acid solution in dioxan (20ml) at room temperature. The solvent was evaporated under reduced pressure to afford the title compound as a white solid, 2.26g.

¹H NMR (400 MHz, DMSO-d₆): δ [ppm] 1.90 (4H, m), 1.98-2.20 (4H, m), 2.40 (2H, m), 2.78 (1H, m), 3.08 (1H, m), 3.80-4.02 (3H, m), 4.40 (1H, m), 7.10 (2H, m), 7.25 (2H, m), 7.42 (2H, m), 7.58 (2H, m), 8.25 (m, 1H), 8.80 (2H, bs), 10.75 (1H, bs).

LRMS: m/z 396.1 (MH⁺).

PREPARATION 81

N-{8-[(3S)-3-endo-Amino-3-phenylpropyl]-8-azabicyclo[3.2.1]oct-3-yl}-3-(4-fluorophenyl)propanamide hydrochloride

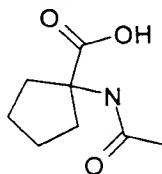


The title compound was obtained as a cream solid (quantitative), from the title compound of preparation 80, following the procedure of preparation 79.

LRMS: m/z (MH⁺) 396.1 (MH⁺).

PREPARATION 82

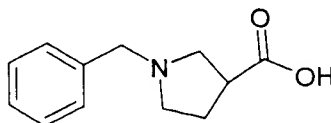
1-(Acetylamino)cyclopentanecarboxylic acid



The title compound was prepared according to the method described in Bull. Soc. Chim. Fr. 1965; 2942.

PREPARATION 83

1-Benzyl-3-pyrrolidinecarboxylic acid



The title compound was prepared according to the method described in J.Org.Chem. 1968; 33; 3637.

PREPARATION 848-Benzyl-N-(4-fluoro-2-nitrophenyl)-8-azabicyclo[3.2.1]octan-3-exo-amine

5 A mixture of the title compound of preparation 26 (7.0g, 32.4mmol), 2, 5-difluoronitrobenzene (5.41g, 34.0mmol) and potassium carbonate (13.4g, 0.97mmol) in dimethylformamide (100ml) was heated to 100°C for 12 hours. The cooled mixture was concentrated under reduced pressure, dissolved in dichloromethane (300ml) and washed with water then brine. The organic layer was dried (MgSO₄) and evaporated under reduced
10 pressure. The residue was purified by column chromatography on silica gel, using an eluent of dichloromethane: methanol (98:2:0) to afford the title compound as a orange solid, 7.6g.

¹H NMR (400MHz, CDCl₃): δ [ppm] 1.74 (4H, m); 1.95 (2H, m); 2.15 (2H, m); 3.34 (2H, s); 3.60 (2H, s); 3.8 (1H, m); 6.82 (1H, m); 7.18-7.42 (6H, m); 7.86 (2H, m).

LRMS: m/z 356.4 (MH⁺).

15

PREPARATION 851-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-4-fluoro-1,2-exo-benzenediamine

 The title compound of preparation 84 (7.6g, 21.41mmol) and 5% palladium on carbon
20 (0.8g) in ethanol (50ml) and tetrahydrofuran (150ml) were stirred under 1 atmosphere of hydrogen for 24 hours at room temperature. The reaction was filtered through arbocel and the solvent removed under reduced pressure to afford the title compound as a dark red oil, 6.0g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.38-1.76 (5H, m); 1.85 (2H, m); 2.06 (2H, m); 3.26 (2H, s); 3.36-3.70 (5H, m); 6.40 (2H, m); 6.60 (1H, m); 7.18-7.40 (5H, m).

25 LRMS: m/z 326.6 (MH⁺).

PREPARATION 861-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl) -exo -5-fluoro -1H-benzimidazole

30 The title compound of preparation 85 (3.0g, 9.22mmol) was refluxed in triethyl orthoformate (20ml) for 16 hours. Excess triethyl orthoformate was evaporated under reduced pressure. The oily residue was taken up in toluene (80ml) refluxed with catalytic para-toluenesulfonic acid for 3 hours and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, using an eluent of dichloromethane:
35 methanol (98:2) to afford the title compound as a light pink solid, 1.91g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.8 (2H, q); 1.98 (2H, m); 2.20-2.36 (4H, m); 3.40 (2H, s); 3.63 (2H, s); 4.56 (1H, m); 7.03 (1H, m); 7.20-7.50 (6H, m); 8.03 (1H, s).

LRMS: m/z 336.3 (MH^+).

PREPARATION 87

1-(8-Azabicyclo[3.2.1]oct-3-yl)-exo-5-fluoro-1H-benzimidazole

5

The title compound of preparation 86 (1.91g, 5.71mmol) in ethanol (80ml) was treated with ammonium formate (2.75g, 43.6mmol) and 20% palladium hydroxide on carbon (500mg) and the mixture was heated to reflux under nitrogen for 5 hours. The cooled mixture was filtered through arboceel and concentrated under reduced pressure. The mixture was dissolved in dichloromethane (100ml) and washed with saturated sodium bicarbonate solution then brine, was dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound as a red oil, 1.23g.

10

1H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.77-2.30 (9H, m); 3.72 (2H, s); 4.52 (1H, m); 7.02 (1H, m); 7.34 (1H, m); 7.44 (1H, dd); 7.98 (1H, s).

15

LRMS: m/z 246.0 (MH^+).

PREPARATION 88

tert-Butyl 1-(1S)-3-[3-exo-(5-fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate

20

The title compound of preparation 88 (1.23g, 5.03mmol) was stirred in dichloromethane (10ml). The title compound of preparation 7 (1.25g, 5.025mmol), sodium triacetoxyborohydride (1.60g, 7.55mmol) and glacial acetic acid (0.30ml) were added, and the solution stirred at room temperature for 16 hours. The reaction mixture was basified with saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane (2x) and the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluent of dichloromethane: methanol (98:2) to afford 1.505g of a light pink solid.

25

1H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.20-1.47 (10H, m); 1.62-1.88 (3H, m); 1.90-2.18 (5H, m); 2.20-2.46 (4H, m); 3.38 (1H, s); 3.60 (1H, s); 4.52 (1H, m); 4.90 (1H, m); 7.0 (2H, m); 7.20-7.50 (5H, m); 7.55 (1H, d); 8.0 (1H, s).

30

LRMS: m/z 479.0 (MH^+).

PREPARATION 89

35

tert-Butyl 3-[(1S)-3-[3-exo-(5-fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]amino)carbonyl]-1-azetidinecarboxylate

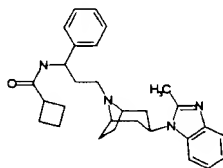
The title compound of preparation 88 (1.505g, 3.15mmol) and 4M hydrochloric acid in dioxane (10ml) were stirred for 1 hour. The excess of solvent was evaporated under reduced pressure to give a cream solid, which was added to the title compound of preparation 61 (0.695g, 3.46mmol), diisopropyl ethylamine (2.2ml, 12.6mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.663g, 3.46mmol), and 1-hydroxybenzotriazole hydrate (0.467g, 3.46mmol) in dichloromethane (20ml). The reaction mixture was stirred at room temperature for 16 hours, concentrated and dissolved in ethyl acetate then washed with 10% sodium carbonate solution. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluent of dichloromethane: methanol (99:4) to afford the title compound as a white powder, 1.182g.

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.4 (10H, m); 1.8 (2H, m); 1.92-2.30 (9H, m); 2.48 (1H, m); 3.15 (1H, m); 3.42 (2H, m); 3.96-4.20 (4H, m); 4.55 (1H, m); 5.20 (1H, q); 7.02 (1H, m); 7.10-7.40 (6H, m); 7.54 (1H, m); 8.0 (1H, s).

LRMS: m/z 489.2 (MH⁺).

Example 1

N-[3-[3-exo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]cyclobutanecarboxamide dihydrochloride

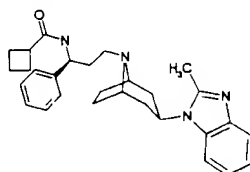


The title compounds of preparation 52 (0.20g, 0.829mmol) and preparation 3 (0.174g, 0.753mmol) were stirred together with sodium triacetoxyborohydride (0.240g, 1.13mmol) and acetic acid (0.05ml, 0.833mmol) in dichloromethane (10ml) under an atmosphere of nitrogen for 24 hours at room temperature. A solution of 10% sodium carbonate was added and the product extracted with dichloromethane. The combined organic extracts were dried (MgSO₄) and the solvent evaporated under reduced pressure. The product was purified by chromatography on silica gel using dichloromethane:methanol (98:2) as eluant, then dissolved in diethyl ether saturated with HCl. Evaporation to dryness provided the title compound, 127mg.

¹H-NMR (400 MHz, CDCl₃): δ [ppm] 1.66-1.80 (4H, m), 1.85-2.23 (10H, m), 2.25-2.40 (2H, m), 2.50-2.58 (2H, m), 2.65 (3H, s), 3.08 (1H, m), 3.44 (2H, m), 4.58 (1H, m), 5.20 (1H, m), 6.85 (1H, d), 7.22 (2H, m), 7.28-7.40 (5H, m), 7.52 (1H, m), 7.68 (1H, m)

LRMS: m/z 457.6 (MH⁺)EXAMPLE 2

N-[(1S)-3-[3-exo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]cyclobutanecarboxamide



Cyclobutane carboxylic acid chloride (224mg, 1.89mmol) was added to the title compound of preparation 67 (646mg, 1.72mmol) and triethylamine (505μl, 3.62mmol) in dichloromethane (10ml). The reaction mixture was stirred at room temperature for 3 hours after which time more triethylamine (500μl, 3.62mmol) and cyclobutane carboxylic acid chloride (104mg, 0.876mmol) were added. Water was added to the mixture, the product was extracted with dichloromethane (2X), the combined organics were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol: 0.88 ammonia (98:2:0.5 to 95:4:1) to afford the title compound as a white powder, 196mg.

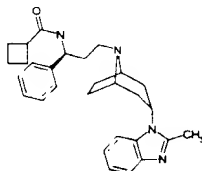
Found C, 73.91; H, 8.08; N, 11.82%

C₂₉H₃₆N₄O; 1H₂O requires C, 73.39; H, 8.07; N, 11.80%

¹H-NMR (400 MHz, CDCl₃): δ [ppm] 1.60-1.80 (4H, m), 1.90-2.20 (9H, m), 2.25-2.40 (3H, m), 2.50-2.58 (2H, m), 2.55-2.65 (4H, m), 3.08 (1H, m), 3.40 (2H, m), 4.58 (1H, m), 5.20 (1H, m), 6.80 (1H, d), 7.18-7.40 (6H, m), 7.50 (1H, m), 7.65 (1H, m)

LRMS: m/z 457.2 (MH⁺)[α]_D -40.0° (c = 0.10, CH₂Cl₂)EXAMPLE 3

N-[(1S)-3-[3-endo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]cyclobutanecarboxamide



The title compound of preparation 68 (565mg, 1.51mmol), cyclobutanecarboxylic acid chloride (207 μl, 1.81mmol), and triethylamine (464 μl, 3.32mmol) were stirred in dichloromethane (15ml) for 18 hours at room temperature. The reaction was diluted with water

and extracted with dichloromethane (2X). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol: 0.88 ammonia (98:1.5:0.5) to afford the title compound as a white solid, 260mg.

5 Found C, 74.13; H, 7.97; N, 11.97%

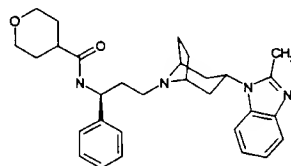
C₂₉H₃₆N₄O; 0.7H₂O requires C, 74.23; H, 8.03; N 11.94%

¹H NMR (400MHz, CDCl₃): δ [ppm] 1.70 (2H, m); 1.82-2.00 (3H, m); 2.10-2.20 (4H, m); 2.22-2.35 (4H, m); 2.47 (5H, m); 2.60 (3H, s); 3.00 (1H, m); 3.40 (2H, bs); 4.75 (1H, m); 5.15 (1H, m); 6.30 (1H, d); 7.18 (2H, m); 7.20-7.30 (6H, m); 7.62 (1H, m)

10 LRMS: m/z 457.4 (MH⁺)

EXAMPLE 4

N-((1S)-3-[3-exo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)tetrahydro-2H-pyran-4-carboxamide



15

The title compound of preparation 67 (86mg, 0.23mmol) in dichloromethane (2.5ml) was added to tetrahydropyran-4-carboxylic acid (30mg, 0.23mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (53mg, 0.28mmol), N-diisopropylethylamine (44μl, 0.25 mmol) and 1-hydroxybenzotriazole hydrate (34mg, 0.25mmol) in dichloromethane (2.5ml). The reaction mixture was stirred for 16 hours at room temperature. The solvent was evaporated under reduced pressure and the residue taken up in ethyl acetate, washed with water, brine, dried (MgSO₄) filtered and evaporated under reduced pressure. The residual pale brown solid was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.25 to 95:5:0.5)

20 to afford the title compound as a white solid, 48mg.

Found C, 70.59; H, 7.83; N, 10.94%

C₃₀H₃₈N₄O₂; 1.3H₂O requires C, 70.64; H, 8.02; N, 10.98%

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.65 (2H, bm), 1.71-1.92 (6H, m), 1.96-2.22 (4H, m), 2.37 (1H, m), 2.46-2.68 (7H, m), 3.39-3.50 (4H, m), 3.98 (2H, m), 4.54 (1H, m), 5.20 (1H, m), 6.79 (1H, m), 7.13-7.21 (2H, m), 7.23-7.30 (1H, m), 7.30-7.40 (4H, m), 7.42-7.54 (1H, m), 7.62-7.72 (1H, m)

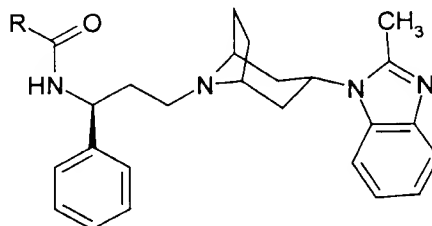
30

LRMS: m/z 487.3 (MH⁺)

Melting point [°C]: 95-96


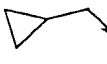
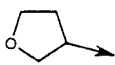
EXAMPLES 5 - 16

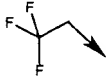
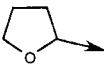
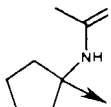
The compounds of the following tabulated examples with the general structure:

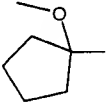
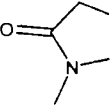


were prepared using a similar method to Example 4 from the title compound of preparation 67 and the corresponding acids.

Example Number	R	yield (%)	Characterization Data
5 1-Acetyl-N- {(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidine carboxamide		1	13.00% Found C, 68.66; H, 7.40; N, 13.30% $C_{30}H_{37}N_5O_2 \cdot 1.5H_2O$ requires C, 68.42; H, 7.66; N, 13.30% 1H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.61-1.84 (4H, m), 1.84 (3H, s), 1.93-2.20 (4H, bm), 2.44-2.71 (7H, m), 3.24 (1H, m), 3.42 (2H, bs), 4.04-4.15 (3H, m), 4.42 (1H, q), 4.56 (1H, m), 5.24 (1H, bm), 7.11-7.21 (6H, m), 7.44-7.56 (1H, m), 7.63-7.73 (1H, m) LRMS: m/z 500.7 (MH^+)
6 1-Hydroxy-N- {(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide		9	10.87% Found C, 71.31; H, 7.58; N, 11.03% $C_{30}H_{38}N_4O_2 \cdot 0.7H_2O \cdot 0.1CH_2Cl_2$ requires C, 71.20; H, 7.86; N, 11.03% 1H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.47-1.92 (10H, m), 1.96-2.14 (5H, m), 2.14-2.28 (2H, m), 2.50 (2H, m), 2.53-2.67 (5H, m), 3.41 (2H, bs), 4.52 (1H, m), 5.20 (1H, m), 7.12-7.23 (2H, m), 7.23-7.30 (1H, m), 7.30-7.41 (4H, m), 7.51-7.60 (1H, m), 7.62-7.70 (1H, m), 7.82 (1H, d).

			LRMS: m/z 487.2 (MH ⁺)
			Melting point [°C]: 90-91
7		4	11.63%
2-Methyl-N- {(1S)-3-[3- <i>exo</i> -(2- methyl-1 <i>H</i> - benzimidazol-1-yl)-8- azabicyclo[3.2.1]oct- 8-yl]-1-phenyl propyl}cyclo propanecarboxamide			Found C, 74.17; H, 8.04; N, C ₂₉ H ₃₆ N ₄ O; 0.75H ₂ O requires C, 74.09; H, 8.04; N, 11.92%
			¹ H NMR (400 MHz, CDCl ₃): δ [ppm] 0.98-1.26 (6H, m), 1.32-1.41 (1H, m), 1.62-1.80 (4H, m), 1.93-2.18 (4H, m), 2.43-2.72 (7H, m), 3.38-3.52 (2H, m), 4.54 (1H, m), 5.20 (1H, q), 7.05 (1H, bd), 7.11-7.22 (2H, m), 7.24-7.30 (1H, m), 7.32-7.40 (4H, m), 7.47-7.54 (1H, m), &.62-7.71 (1H, m)
			LRMS: m/z 457.6 (MH ⁺)
			Melting point [°C]: 105-106
8		3	11.77%
2- Cyclopropyl-N-[(1S)- 3-[3- <i>exo</i> -(2-methyl- 1 <i>H</i> -benzimidazol-1- yl)-8-azabicyclo [3.2.1]oct-8-yl]-1- phenylpropyl] acetamide			Found C, 73.28; H, 7.99; N, C ₂₉ H ₃₆ N ₄ O; 1H ₂ O requires C, 73.39; H, 8.07; N, 11.88%
			¹ H NMR (400 MHz, CDCl ₃): δ [ppm] 0.21 (2H, m), 0.61 (2H, m), 0.97- 1.08 (1H, m), 1.61-1.80 (4H, m), 1.96- 2.14 (4H, bm), 2.21 (2H, m), 2.44-2.68 (7H, m), 3.42 (2H, bs), 4.54 (1H, m), 5.24 (1H, m), 6.88 (1H, d), 7.16-7.22 (2H, m), 7.24-7.30 (1H, m), 7.32-7.41 (4H, m), 7.47-7.56 (1H, m), 7.62-7.70 (1H, m)
			LRMS: m/z 456.9 (MH ⁺)
			Melting point [°C]: 85-86
9		6	11.41%
N-[(1S)-3-[3- <i>exo</i> -(2-methyl-1 <i>H</i> - benzimidazol-1-yl)-8- azabicyclo [3.2.1]oct- 8-yl]-1-phenylpropyl] tetrahydro-3-			Found C, 70.92; H, 7.73; N, C ₂₉ H ₃₆ N ₄ O ₂ ; 1H ₂ O requires C, 70.99; H, 7.81; N, 11.42%
			¹ H NMR (400 MHz, CDCl ₃): δ [ppm] 1.68 (2H, bm), 1.73 (2H, d), 1.94- 2.26 (6H, m), 2.48-2.56 (3H, m), 2.56-

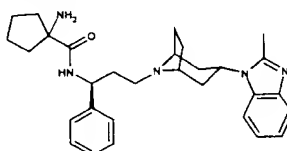
furancarboxamide	2.68 (4H, m), 2.92 (1H, bm), 3.43 (2H, bs), 3.76-3.84 (1H, m), 3.86-4.01 (3H, m), 4.56 (1H, m), 5.21 (1H, m), 7.03-7.12 (1H, bm), 7.13-7.23 (2H, m), 7.23-7.40 (5H, m), 7.45-7.54 (1H, m), 7.64-7.72 (1H, m) LRMS: m/z 473.6 (MH ⁺) Melting point [°C]: 93-94
10 3,3,3-Trifluoro- <i>N</i> -{(1 <i>S</i>)-3-[3- <i>exo</i> -(2-methyl-1 <i>H</i> -benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]-1-phenylpropyl} propanamide	<div style="display: flex; align-items: center; justify-content: center;">  <div style="margin: 0 10px;">2</div> </div> Found C, 66.18; H, 6.51; N, 11.33% C ₂₇ H ₃₁ F ₃ N ₄ O; 0.3H ₂ O requires C, 66.19; H, 6.50; N, 11.43% ¹ H NMR (400 MHz, CDCl ₃): δ [ppm] 1.67 (2H, d), 1.76 (2H, d), 2.01 (1H, m), 2.06-2.18 (3H, m), 2.47-2.68 (7H, m), 3.10 (2H, q), 3.44 (2H, bm), 4.54 (1H, m), 5.22-5.31 (1H, m), 7.14-7.22 (2H, m), 7.22-7.34 (3H, m), 7.34-7.40 (2H, m), 7.43-7.54 (2H, m), 7.64-7.72 (1H, m) LRMS: m/z 485.3 (MH ⁺)
11 <i>N</i> -{(1 <i>S</i>)-3-[3- <i>exo</i> -(2-Methyl-1 <i>H</i> -benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]-1-phenylpropyl} tetrahydro-2-furancarboxamide	<div style="display: flex; align-items: center; justify-content: center;">  <div style="margin: 0 10px;">3</div> </div> Found C, 71.06; H, 7.66; N, 11.08% C ₂₉ H ₃₆ N ₄ O ₂ ·1H ₂ O requires C, 70.99; H, 7.81; N, 11.42% ¹ H NMR (400 MHz, CDCl ₃): δ [ppm] 1.58-1.76 (4H, bm), 1.79-1.94 (2H, m), 1.98-2.16 (5H, bm), 2.20-2.35 (1H, m), 2.40-2.67 (7H, bm), 3.32-3.47 (2H, bm), 3.81-4.00 (2H, m), 4.26-4.44 (1H, m), 4.52 (1H, m), 5.13-5.33 (1H, m), 7.12-7.23 (2H, m), 7.26-7.42 (5H, m), 7.47-7.58 (1H, m), 7.57-7.71 (1H, m) LRMS: m/z 473.0 (MH ⁺)
12 1-(Acetylamino)- <i>N</i> -	<div style="display: flex; align-items: center; justify-content: center;">  <div style="margin: 0 10px;">0</div> </div> Found C, 66.86; H, 7.34; N, 12.21% C ₃₂ H ₄₁ N ₅ O ₂ ·0.7CH ₂ Cl ₂ requires

<p>{(1S)-3-[3-<i>exo</i>-(2-methyl-1<i>H</i>-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl} cyclopentane carboxamide</p>	<p>C, 66.89; H, 7.28; N, 11.93%</p> <p>¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.46-1.82 (5H, bm), 1.88-2.19 (11H, m), 2.19-2.42 (3H, bm), 2.42-2.76 (8H, bm), 3.44 (2H, bs), 4.52 (1H, m), 5.09 (1H, m), 5.72 (1H, bs), 7.16-7.23 (2H, m), 7.28-7.40 (4H, m), 7.59 (1H, bs), 7.63-7.70 (1H, m), 7.92 (1H, bd)</p> <p>LRMS: m/z 528.6 (MH⁺)</p>
<p>13</p> <p>$\xrightarrow{\text{CH}_3}$</p> <p><i>N</i>-{(1S)-3-[3-<i>exo</i>-(2-Methyl-1<i>H</i>-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide (by-product in Example 5)</p>	<p>Found C, 74.09; H, 7.84; N, 13.10%</p> <p>C₂₆H₃₂N₄O;0.3H₂O requires C, 74.01; H, 7.79; N, 13.28%</p> <p>¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.64-1.80 (4H, m), 1.92-2.18 (7H, m), 2.43-2.57 (3H, m), 2.60-2.68 (4H, m), 3.37-3.52 (3H, m), 4.54 (1H, m), 5.23 (1H, m), 7.12-7.21 (3H, m), 7.30-7.42 (4H, m), 7.50 (1H, m), 7.68 (1H, m)</p> <p>LRMS: m/z 417.5 (MH⁺)</p>
<p>14</p> <p>1-Methoxy-<i>N</i>-{(1S)-3-[3-<i>exo</i>-(2-methyl-1<i>H</i>-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl} cyclopentane carboxamide</p>	<p> 6</p> <p>Found C, 71.95; H, 8.11; N, 10.77%</p> <p>C₃₁H₄₀N₄O₂;0.9H₂O requires C, 72.03; H, 8.15; N, 10.84%</p> <p>¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.61-1.80 (8H, m), 1.81-1.94 (2H, m), 1.94-2.20 (7H, m), 2.43-2.67 (7H, m), 3.23 (3H, s), 3.43 (2H, bs), 4.54 and 4.85 (1H, 2 x m), 5.19 (1H, m), 7.13-7.22 (2H, m), 7.23-7.28 (1H, m), 7.29-7.40 (4H, m), 7.56-7.64 (1H, m), 7.68 (1H, m)</p> <p>LRMS: m/z 501.9 (MH⁺)</p>
<p>15</p> <p>1-Methyl-<i>N</i>-{(1S)-3-[3-<i>exo</i>-(2-methyl-1<i>H</i>-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl} cyclopentane carboxamide</p>	<p> 5</p> <p>Found C, 67.53; H, 7.66; N, 12.99%</p> <p>C₃₀H₃₇N₅O₂;2H₂O requires C, 67.27; H, 7.71; N, 13.07%</p>

imidazol-1-	¹ H NMR (400 MHz, CDCl ₃): δ
yl)-8-	[ppm] 1.64-1.72 (2H, m), 1.78 (2H, d),
azabicyclo[3.2.1]	1.95-2.18 (4H, m), 2.45-2.78 (9H, m),
oct-8-yl]-1-	2.83 (3H, s), 3.07 (1H, m), 3.40-3.54 (3H,
phenyl	m), 3.62-3.76 (1H, m), 4.56 (1H, m), 5.22
propyl)-2-	(1H, q), 7.12-7.24 (3H, m), 7.31 (3H, m),
oxo-4-	7.34-7.41 (2H, m), 7.48 (1H, m), 7.68
pyrrolidinecarbox	(1H, m)
amide	LRMS: m/z 500.5 (MH ⁺)

EXAMPLE 16

1-Amino-N-((1S)-3-exo-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)cyclopentanecarboxamide



5

The title compound of preparation 72 (135mg, 0.23mmol) and trifluoroacetic acid (2ml) in dichloromethane (5ml) were stirred for 16 hours. The solvent was evaporated under reduced pressure and the residue quenched with aqueous saturated sodium carbonate solution. This aqueous solution was extracted with dichloromethane (3x) and the combined organic extracts washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. The residual pale brown solid was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.25 to 95:5:0.5) to afford the title compound as a white solid, 96mg.

Found C, 71.87; H, 8.26; N, 14.03%
 C₃₀H₃₉N₅O;0.9H₂O requires C, 71.80; H, 8.19; N, 13.95%

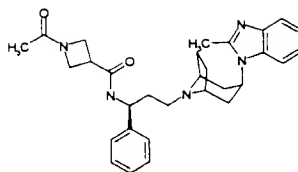
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.27-1.89 (11H, m), 1.89-2.18 (5H, m), 2.18-2.35 (2H, m), 2.41-2.53 (2H, m), 2.55-2.66 (5H, m), 3.40 (2H, bs), 4.52 and 4.77 (1H, 2 x m), 5.06-5.18 (1H, m), 7.12-7.22 (2H, m), 7.22-7.33 (1H, m), 7.33-7.39 (4H, m), 7.52-7.59 (1H, m), 7.63-7.71 (1H, m), 8.24 and 8.43 (1H, 2 x m)

LRMS: m/z 486.9 (MH⁺)

20

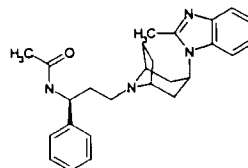
EXAMPLES 17 and 18

1-Acetyl-N-((1S)-3-[3-endo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide



and

N-((1S)-3-[3-endo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)acetamide



5

1-(3-Dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (100mg, 0.52mmol) was added to a solution of the title compound of preparation 68 (150mg, 0.40mmol) and 1-acetyl-3-azetidinecarboxylic acid (69mg, 0.48mmol) in dichloromethane (10ml). The reaction mixture was stirred for 3 hours after which time the solution was evaporated to dryness, re-
 10 dissolved in ethyl acetate, washed with a saturated aqueous sodium carbonate solution, then water. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (95:5:0.5) as eluant to afford the title compound of example 17 as a white foam (75mg),

15 Found C, 67.96; H, 7.44; N, 13.09%

C₃₀H₃₇N₅O₂·1.6H₂O requires C, 68.18; H, 7.67; N, 13.25%

¹H-NMR (400 MHz, CDCl₃): δ [ppm] 1.68-1.80 (2H, m), 1.87 (3H, s), 1.92-2.31 (8H, m), 2.40-2.48 (2H, m), 2.63 (3H, s), 3.10 (1H, m), 3.36-3.47 (2H, m), 4.00-4.22 (3H, m), 4.37-4.46 (1H, m), 4.68-4.80 (1H, m), 5.20 (1H, m), 6.13 (1H, bd), 7.15-7.41 (8H, m), 7.67 (1H, m)

20 LRMS: m/z 500.4 (MH⁺)

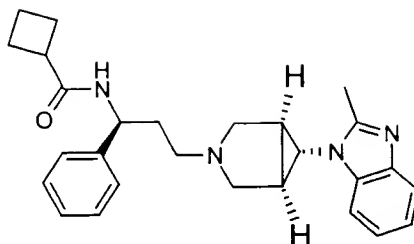
and the title compound of example 18, 20mg.

¹H-NMR (400 MHz, CDCl₃): δ [ppm] 1.71-1.84 (2H, m), 1.96-2.03 (7H, m), 2.05-2.33 (4H, m), 2.40-2.58 (2H, m), 2.63 (3H, m), 3.38-3.42 (2H, m), 4.72 (1H, m), 5.19 (1H, m), 6.34 (1H, d), 7.14-7.40 (8H, m), 7.64 (1H, m)

25 LRMS: m/z 417.2 (MH⁺)

EXAMPLE 19

N-((1S)-3-[6-(2-Methyl-1H-benzimidazol-1-yl)-3-azabicyclo[3.1.0]hex-3-yl]-1-phenylpropyl)cyclobutanecarboxamide



The title compounds of preparation 55 (0.056g, 0.262mmol) and preparation 8 (0.091g, 0.394mmol) were stirred together with sodium triacetoxyborohydride (0.083g, 0.394mmol) and acetic acid (0.015ml, 0.262mmol) in dichloromethane (10ml) under an atmosphere of nitrogen for 4 hours at room temperature. A saturated aqueous solution of sodium bicarbonate was added and the product extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried (MgSO_4) and the solvent evaporated under reduced pressure. The product was purified by column chromatography on silica gel using ethyl acetate:methanol:0.88 ammonia (97.5:2.5:0.25) as eluant, then dissolved in acetonitrile/water and freeze-dried to provide the title compound, 50mg.

Found C, 73.35; H, 7.65; N, 12.51%

$\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}; 0.75\text{H}_2\text{O}$; requires C, 73.36; H, 7.64; N, 12.67%

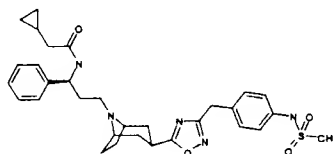
$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ [ppm] 1.80-2.20 (8H, m), 2.20-2.36 (2H, m), 2.40-2.56 (4H, m), 2.63 (3H, s), 2.88-3.00 (1H, m), 3.37-3.42 (3H, m), 5.06 (1H, m), 6.20 (1H, m), 7.18-7.38 (7H, m), 7.40 (1H, m), 7.64 (1H, m)

LRMS: m/z 429.4 (MH^+)

$[\alpha]_D -39.4$ ($c = 0.10$, CH_3OH)

EXAMPLE 20

2-Cyclopropyl-N-[(1S)-3-[3-exo-(3-{4-[(methylsulphonyl)amino]benzyl}-1,2,4-oxadiazol-5-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]acetamide trifluoroacetate



The title compound of preparation 64 (392mg, 6.58mmol) and 4M hydrochloric acid in dioxan (10ml) were stirred for 1 hour and the reaction concentrated under reduced pressure. The residue was partitioned between dichloromethane and aqueous sodium carbonate solution and the aqueous layer was extracted with dichloromethane (2X). The combined organic solutions were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure. The resulting colorless oil (150mg, 0.302mmol), cyclopropane acetic acid (36mg, 0.363mmol), and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride

(70mg, 0.363mmol) in dichloromethane (5ml) were stirred at room temperature for 16 hours. The reaction was basified with 10% aqueous sodium carbonate solution and extracted with dichloromethane. The organic layer was washed with water, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 96:4), then purification by reverse phase preparative HPLC, using an elution gradient of 0.1% trifluoroacetic acid in water:acetonitrile (90:10 to 10:90), to afford the title compound as a white solid, 44mg.

Found C, 55.09; H, 5.77; N, 9.43%

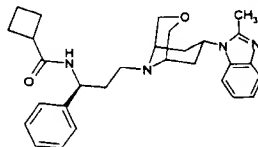
C₃₁H₃₉N₅O₄S; 1.5 H₂O; 1CF₃CO₂H requires C, 55.14; H, 6.03; N 9.74%

¹H NMR (400MHz, CDCl₃): δ [ppm] 0.18 (2H, m); 0.55 (2H, m); 1.05 (1H, m); 1.62 (2H, m); 1.70-2.10 (11H, bm); 2.18 (2H, d); 2.40 (2H, m); 3.00 (2H, s); 3.23 (2H, m); 3.40 (1H, bs); 4.00 (1H, s); 5.20 (1H, m); 7.10-7.30 (9H, m); 8.40 (1H, bs)

LRMS: m/z 578.3 (MH⁺)

EXAMPLE 21

N-[(1S)-3-[7-exo-(2-Methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl]cyclobutanecarboxamide



The title compound of preparation 70 (200mg, 0.4mmol) in dichloromethane (2.5ml) was added to cyclobutanecarboxylic acid chloride (57mg, 0.48mmol), and N-diisopropylethylamine (313μl, 1.8mmol) in dichloromethane (2.5ml). The reaction mixture was stirred at room temperature for 3 hours, then washed with water and brine. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluant of dichloromethane: methanol (98:2) to afford the title compound as a white powder, 43.2mg.

Found C, 71.32; H, 7.74; N, 11.31%

C₂₉H₃₆N₄O₂; 1H₂O requires C, 70.99; H, 7.81; N 11.42%

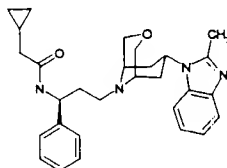
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.75 (2H, m); 1.90 (1H, m); 1.95-2.10 (3H, m); 2.15 (2H, m); 2.30 (2H, m); 2.62 (3H, s); 2.65-2.78 (2H, m); 2.82 (2H, m); 2.92 (2H, d); 3.02 (1H, m); 3.95 (3H, m); 4.02 (1H, t); 5.28 (1H, m); 5.62 (1H, m); 6.50 (1H, d); 7.18 (2H, m); 7.30-7.40 (6H, m); 7.70 (1H, d)

LRMS: m/z 473.2(MH⁺)

[α]_D -31.5 (c = 0.54, MeOH)

EXAMPLE 22

2-Cyclopropyl-N-[(1S)-3-[7-exo-(2-methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl]acetamide



5

The title compound of preparation 70 (200mg, 0.4mmol) in dichloromethane (2.5ml) was added to cyclopropane acetic acid (48mg, 0.48mmol), N-diisopropylethylamine (312μl, 1.8 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (77mg, 0.40mmol), and 1-hydroxybenzotriazole hydrate (61mg, 0.40mmol) in dichloromethane (2.5ml). The reaction mixture was stirred at room temperature for 16 hours, then washed with 10% aqueous sodium carbonate solution. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 97:3) to afford the title compound as a white powder, 109mg.

15

Found C, 71.52; H, 7.81; N, 11.41%

C₂₉H₃₆N₄O₄·0.8H₂O requires C, 71.52; H, 7.78; N 11.50%

¹H NMR (400 MHz, CDCl₃): δ [ppm] 0.20 (2H, m); 0.6 (2H, m); 1.00 (1H, m); 1.75 (2H, dd); 1.95-2.10 (2H, m); 2.18 (2H, d); 2.62 (3H, s); 2.65-2.90 (5H, m); 2.95 (1H, s); 3.92 (2H, m); 3.95 (1H, s); 4.00 (1H, t); 5.30 (1H, m); 5.62 (1H, m); 6.62 (1H, d); 7.15 (2H, m); 7.30-7.40 (6H, m); 7.65 (1H, d)

20

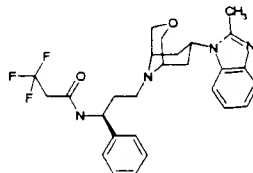
LRMS: m/z 473.3 (MH⁺)

[α]_D -29 (c = 1, MeOH)

EXAMPLE 23

25

3,3,3-Trifluoro-N-[(1S)-3-[7-exo-(2-methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl]propanamide



The title compound of preparation 70 (200mg, 0.4mmol) in dichloromethane (2.5ml) was added to 3,3,3-trifluoropropionic acid (62mg, 0.48mmol), N-diisopropylethylamine (312μl, 1.8 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (77mg, 0.40mmol),

30

and 1-hydroxybenzotriazole hydrate (61mg, 0.40mmol) in dichloromethane (2.5ml). The reaction mixture was stirred at room temperature for 24 hours, then washed with 10% aqueous sodium carbonate solution. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 97:3) to afford the title compound as a white powder, 146mg.

Found C, 63.14; H, 6.33; N, 10.89%

C₂₇H₃₁N₄F₃O₂·0.7H₂O requires C, 63.19; H, 6.36; N 10.92%.

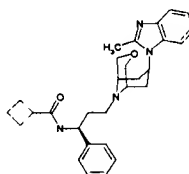
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.75 (2H, m); 2.08 (2H, m); 2.62 (3H, s); 2.64-2.80 (2H, m); 2.82 (2H, m); 2.92 (2H, s); 3.10 (2H, m); 3.95 (3H, m); 4.05 (1H, m); 5.35 (1H, m); 5.62 (1H, m); 7.10-7.20 (3H, m); 7.30 (3H, m); 7.35 (3H, m); 7.70 (1H, d)

LRMS: m/z 501.1 (MH⁺)

[α]_D -30 (c = 1, MeOH)

EXAMPLE 24

N-((1S)-3-[7-endo-(2-Methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl)cyclobutanecarboxamide



The title compound of preparation 69 (200mg, 0.51mmol) in dichloromethane (2.5ml) was added to cyclobutanecarboxylic acid chloride (57μl, 0.61mmol), N-diisopropylethylamine (133μl, 0.76 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (99mg, 0.51mmol), and 1-hydroxybenzotriazole hydrate (79mg, 0.51mmol) in dichloromethane (2.5ml). The reaction mixture was stirred at room temperature for 16 hours, then basified with 10% aqueous sodium carbonate solution, and the phases separated. The aqueous layer was extracted with dichloromethane (2X). The combined organics were washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 96:4) to afford the title compound as a white solid, 133mg.

Found C, 71.67; H, 7.79; N, 11.46%

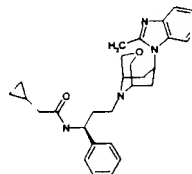
C₂₉H₃₆N₄O₂·0.7H₂O requires C, 71.78; H, 7.77; N 11.55%

¹H NMR (400MHz, CDCl₃): δ [ppm] 1.85 (1H, m); 1.95 (3H, m); 2.10 (2H, m); 2.28 (4H, m); 2.58 (2H, t); 2.64 (3H, s); 2.75 (2H, m); 3.00 (3H, m); 3.45 (2H, d); 3.90 (2H, t); 4.85 (1H, m); 5.20 (1H, d); 5.82 (1H, d); 7.20 (2H, m); 7.30 (3H, m); 7.38 (2H, m); 7.70 (1H, m); 7.79 (1H, m)

LRMS: m/z 473.7 (MH^+) $[\alpha]_D -44$ ($c = 2$, MeOH)**EXAMPLE 25**

5

2-Cyclopropyl-N-((1S)-3-[7-endo-(2-methyl-1H-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl)acetamide



The title compound of preparation 69 (200mg, 0.51mmol) in dichloromethane (2.5ml) was added to cyclopropane acetic acid (58 μ l, 0.61mmol), N-diisopropylethylamine (133 μ l, 0.76 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (99mg, 0.51mmol), and 1-hydroxybenzotriazole hydrate (79mg, 0.51mmol) in dichloromethane (2.5ml). The reaction mixture was stirred at room temperature for 16 hours, then basified with saturated aqueous sodium carbonate solution. The phases were separated and the aqueous layer was extracted with dichloromethane (2X). The combined organics were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 96:4) to afford the title compound as a white solid, 209mg.

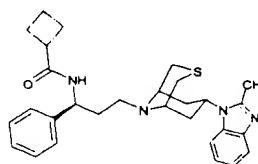
Found C, 71.37; H, 7.81; N, 11.44%.

 $C_{29}H_{36}N_4O_2 \cdot 1H_2O$ requires C, 70.99; H, 7.81; N 11.42%

1H NMR (400MHz, $CDCl_3$): δ [ppm] 0.2 (2H, m); 0.6 (2H, m); 0.95 (1H, m); 2.02 (2H, m); 2.19 (2H, m); 2.32 (2H, m); 2.58 (2H, m); 2.65 (3H, s); 2.78 (2H, m); 2.95 (1H, d); 3.05 (1H, d); 3.42 (2H, d); 3.90 (2H, t); 4.90 (1H, m); 5.27 (1H, m); 6.22 (1H, d); 7.20 (2H, m); 7.30 (3H, m); 7.38 (2H, m); 7.68 (1H, m); 7.78 (1H, m)

LRMS: m/z 474.4 (MH^+) $[\alpha]_D -40$ ($c = 2$, MeOH)**EXAMPLE 26**

N-((1S)-3-[7-exo-(2-Methyl-1H-benzimidazol-1-yl)-3-thia-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl)cyclobutanecarboxamide



The title compound of preparation 66 (0.936g, 1.85mmol) and 4M hydrochloric acid in dioxan (10ml) were stirred for 1 hour. The excess of solvent was evaporated under reduced pressure to give a cream solid, which was added to cyclobutanecarboxylic acid (0.2ml, 2.03mmol), N-diisopropylethylamine (1.6ml, 9.2mmol), 1-(3-dimethylaminopropyl)-3-ethyl-
 5 carbodiimide hydrochloride (390mg, 2.03mmol), and 1-hydroxybenzotriazole hydrate (275mg, 2.03mmol) in dichloromethane (5ml). The reaction mixture was stirred at room temperature for 16 hours, concentrated under reduced pressure and dissolved in ethyl acetate then washed with 10% aqueous sodium carbonate solution. The organic layer was dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column
 10 chromatography on silica gel, using an eluant of dichloromethane: methanol (99:1) to afford the title compound as a white powder, 656mg.

Found C, 69.84; H, 7.45; N, 11.17%

C₂₉H₃₆N₄OS·0.6H₂O requires C, 69.77; H, 7.51; N 11.22%

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.80-2.50 (12H, m); 2.63 (3H, s); 2.70-2.95 (4H, m); 3.05 (1H, m); 3.20-3.50 (4H, m); 5.25 (1H, d); 6.35 (1H, d), 6.70 (1H, m); 7.0-7.4 (7H, m);
 15 7.45 (1H, m); 7.70 (1H, m)

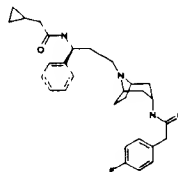
LRMS: m/z 489.2 (MH⁺)

[α]_D -31.5 (c = 1, MeOH)

20

EXAMPLE 27

2-Cyclopropyl-N-[(1S)-3-(3-endo-[2-(4-fluorophenyl)acetyl]amino)-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl]acetamide



The title compound of preparation 81 (0.2g, 0.42mmol) was added to cyclopropane
 25 acetic acid (51mg, 0.52mmol), N-diisopropylethylamine (0.26ml, 1.47 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (82mg, 0.42mmol), and 1-hydroxybenzotriazole hydrate (66mg, 0.42mmol) in dichloromethane (10ml). The reaction mixture was stirred at room temperature for 16 hours, then washed with a saturated aqueous sodium carbonate solution. The organic layer was dried (MgSO₄), filtered and evaporated
 30 under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol (98:2 to 97:3) to afford the title compound as a white powder, 40mg.

Found C, 70.73; H, 7.54; N, 8.47%

C₂₉H₃₆FN₃O₂·0.8H₂O, requires C, 70.79; H, 7.54; N, 8.54%.

^1H NMR (400 MHz, CDCl_3): δ [ppm] 0.18 (2H, m); 0.55 (2H, m); 1.0 (1H, m); 1.20 (2H, m); 1.5 (2H, m); 1.6-2.0 (4H, m); 2.0-2.2 (4H, m); 2.2-2.4 (2H, m); 3.1 (1H, s); 3.25 (1H, s); 3.55 (2H, s); 4.1 (1H, m); 5.1 (1H, m); 5.7 (1H, d); 7.0-7.1 (2H, m); 7.2-7.4 (7H, m); 7.8 (1H, d)

LRMS: m/z 478.4 (MH^+)

5 $[\alpha]_D -36.0$ ($c = 1.0$, MeOH)

EXAMPLE 28

N-[(1*S*)-3-(3-[[3-*endo*-(4-Fluorophenyl)propanoyl]amino]-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl]cyclobutanecarboxamide

10

The title compound of preparation 81 (0.3g, 0.640mmol) was added to cyclobutanecarboxylic acid chloride (0.084ml, 0.735mmol) and *N*-diisopropylethylamine (0.38ml, 2.18 mmol) in dichloromethane (10ml). The reaction mixture was stirred at room temperature for 2 hours and basified with saturated aqueous sodium carbonate solution. The phases were separated and the aqueous layer was extracted with dichloromethane (2X). The combined organic solutions were washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol: 0.88 ammonia (98:2:0 to 95.5:4:0.5) to afford the title compound as a white powder, 80mg.

20

Found C, 70.40; H, 7.61; N, 8.12 %

$\text{C}_{29}\text{H}_{36}\text{FN}_3\text{O}_2 \cdot \text{H}_2\text{O}$ requires C, 70.28; H, 7.73; N, 8.48%

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.20 (2H, m); 1.55 (2H, m); 1.75-2.40 (14H, m); 3.0 (1H, q); 3.15 (1H, s); 3.25 (1H, s); 3.65 (2H, s); 4.10 (1H, m); 5.10 (1H, m); 5.7 (1H, m); 7.10 (2H, m); 7.15-7.3 (7H, m); 8.9 (1H, s)

25

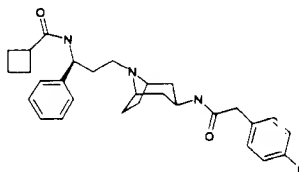
LRMS: m/z 478.0 (MH^+)

$[\alpha]_D -46.4$ ($c = 1.0$, MeOH)

EXAMPLE 29

N-[(1*S*)-3-(3-[[3-*exo*-(4-Fluorophenyl)propanoyl]amino]-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl]cyclobutanecarboxamide

30



The title compound was obtained as a white powder (30%), from the compound of preparation 80 (0.2g, 0.42mmol) and cyclobutanecarboxylic acid, following the procedure described in example 28.

Found C, 71.36; H, 7.64; N, 8.54%

C₂₉H₃₆N₃O₂·0.6H₂O requires C, 71.31; H, 7.68; N, 8.60%

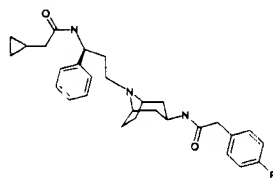
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.22-1.40 (2H, m); 1.65 (2H, m); 1.75-2.35 (14H, m); 2.90 (1H, m); 3.20 (1H, s); 3.25 (1H, s); 3.50 (2H, s); 4.10 (1H, m); 5.10 (2H, m); 7.05 (2H, m); 7.18-7.30 (7H, m); 7.50 (1H, d)

LRMS: m/z 478.5 (MH⁺)

[α]_D -20 (c = 0.4, MeOH)

EXAMPLE 30

10 2-Cyclopropyl-N-[(1S)-3-(3-exo-{[2-(4-fluorophenyl)acetyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl]acetamide



The title compound was obtained as a white powder (20%), from the compound of preparation 80 (0.2g, 0.42mmol) and cyclopropane acetic acid (51mg, 0.52mmol), following the procedure of example 27.

Found C, 71.06; H, 7.67; N, 8.48%

C₂₉H₃₆FN₃O₂·0.7H₂O requires C, 71.05; H, 7.69; N 8.57%

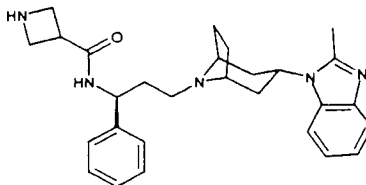
¹H NMR (400 MHz, CDCl₃): δ [ppm] 0.15 (2H, m); 0.58 (2H, m); 0.95 (1H, m); 1.25-1.40 (2H, m); 1.70 (2H, m); 1.75-1.98 (7H, m); 2.10 (2H, m); 2.30 (2H, m); 3.20 (2H, d); 3.45 (2H, s); 4.10 (1H, m); 5.10 (2H, m); 7.00 (2H, m); 7.15-7.35 (7H, m)

LRMS: m/z 477.9 (MH⁺)

[α]_D -30 (c = 0.4, MeOH)

EXAMPLE 31

25 N-[(1S)-3-[3-exo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-azetidinecarboxamide



The title compound was obtained from the title compound of preparation 71 as a clear glass in 64% yield using a similar procedure to that described in preparation 52 (alternative method).

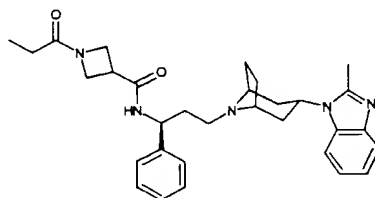
Found C, 68.29; H, 7.64; N, 14.01%

C₂₈H₃₅N₅O₂·2H₂O requires C, 68.13; H, 7.96; N, 14.19%

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.56-1.91 (5H, m), 1.97-2.20 (4H, m), 2.44-2.71 (7H, m), 3.31-3.54 (3H, m), 3.68-3.80 (2H, m), 3.84-3.96 (2H, m), 4.44-4.61 (1H, m), 5.15-5.28 (1H, m), 7.12-7.41 (7H, m), 7.44-7.57 (1H, m), 7.61-7.74 (1H, m)
LRMS: m/z 458.7 (MH⁺)

EXAMPLE 32

N-((1S)-3-[3-exo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-1-propionyl-3-azetidinecarboxamide



Propionyl chloride (14μl, 0.16mmol) was added to a solution of the title compound of example 31 (70mg, 0.15mmol) and triethylamine (24μl, 0.17mmol) in dichloromethane (6ml). The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure and the residue taken up in ethyl acetate, washed with brine, dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.25 to 90:5:0.5) to afford the title compound as a white solid, 29mg.

Found C, 67.72; H, 7.85; N, 12.48%

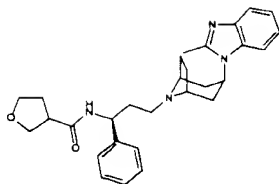
C₃₁H₃₉N₅O₂·2H₂O requires C, 67.73; H, 7.88; N, 17.74%

¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.08 (3H, t), 1.76 (2H, d), 1.94-2.18 (7H, bm), 2.44-2.67 (8H, bm), 3.26 (1H, m), 3.44 (2H, bs), 4.05-4.24 (3H, m), 4.41 (1H, m), 4.56 (1H, m), 5.24 (1H, m), 7.15-7.23 (2H, m), 7.28-7.43 (6H, m), 7.48 (1H, m), 7.63-7.71 (1H, d)

LRMS: m/z 514.6 (MH⁺)

EXAMPLE 33

N-((1S)-3-[3-endo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)tetrahydro-3-furancarboxamide



The title compound of preparation 68 (110mg, 0.29mmol), tetrahydro-3-furanoic acid (36mg, 0.31mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (62mg, 0.32mmol) were stirred together for 30 minutes at room temperature in 5ml of dichloromethane. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium carbonate solution then water. The organic phase was dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified using column chromatography on silica gel using an eluant of dichloromethane:methanol:0.88 ammonia (98:2:0.25) to afford the title compound as white foam, 69mg.

Found C, 71.40; H, 7.82; N, 11.62%

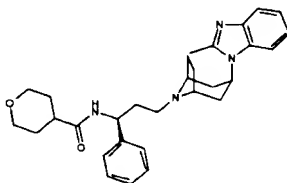
$\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_2 \cdot 0.9 \text{ H}_2\text{O}$ requires C, 71.25; H, 7.79; N, 11.46%

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.68-1.81 (2H, m), 1.92-2.06 (4H, m), 2.06-2.32 (7H, m), 2.39-2.53 (2H, m), 2.58-2.65 (3H, m), 2.85-2.97 (1H, m), 3.35-3.45 (2H, m), 3.77-3.85 (1H, m), 3.85-3.98 (3H, m), 4.69-4.80 (1H, m), 5.13-5.23 (1H, m), 6.29-6.40 (1H, m), 7.15-7.23 (2H, m), 7.23-7.42 (5H, m), 7.65-7.73 (1H, m)

LRMS: m/z 473.0 (MH^+)

EXAMPLE 34

N-((1S)-3-((3-endo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl)tetrahydro-2H-pyran-4-carboxamide



The title compound was obtained from the title compound of preparation 68 and tetrahydro-2H-pyran-4-carboxylic acid in 41% yield using a similar procedure to that described in example 33.

Found C, 71.93; H, 7.96; N, 11.29%

$\text{C}_{30}\text{H}_{38}\text{N}_4\text{O}_2 \cdot 0.8 \text{ H}_2\text{O}$ requires C, 71.91; H, 7.97; N, 11.18%

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.68-1.90 (6H, m), 1.94-2.03 (4H, m), 2.06-2.19 (2H, m), 2.19-2.52 (5H, m), 2.63 (3H, s), 3.32-3.45 (4H, m), 3.98-4.05 (2H, m), 4.68-4.81 (1H,

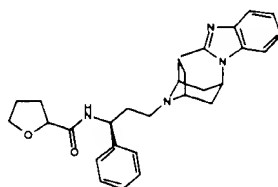
m), 5.13-5.23 (1H, m), 5.92-5.97 (1H, d), 7.13-7.23 (2H, m), 7.26-7.40 (6H, m), 7.65-7.68 (1H, m)

LRMS: m/z 487.0 (MH⁺)

5

EXAMPLE 35

N-((1S)-3-[3-endo-(2-Methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)tetrahydro-2-furancarboxamide



The title compound was prepared in 67% yield from the title compound of preparation 68 and tetrahydro-2-furanoic acid using a similar method to that described in example 33.

Found C, 71.78; H, 7.73; N, 11.63%

C₂₉H₃₆N₄O₂·0.7H₂O requires C, 71.78; H, 7.77; N, 11.55%

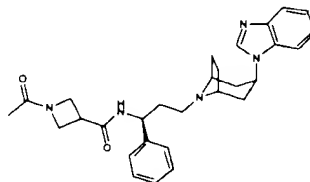
¹H NMR (400 MHz, CDCl₃): δ [ppm] 1.68-2.35 (12H, m), 2.39-2.55 (2H, m), 2.58-2.65 (3H, m), 3.32-3.45 (2H, m), 3.84-4.00 (4H, m), 4.32-4.39 and 4.39-4.45 (1H, m), 4.74-4.87 (1H, m), 5.13-5.23 (1H, m), 7.13-7.23 (2H, m), 7.23-7.32 (2H, m), 7.32-7.39 (5H, m), 7.65-7.71 (1H, m)

LRMS: m/z 473.0 (MH⁺)

20

EXAMPLE 36

1-Acetyl-N-((1S)-3-[3-endo-(1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide



The title compound of preparation 73 (730mg, 1.34mmol) was stirred for 8 hours at room temperature in a 10ml mixture of dichloromethane:trifluoroacetic acid (4:1). The solvents were removed under reduced pressure. The residue was basified with saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane (x4). The combined organic layers were dried (MgSO₄), filtered and evaporated under reduced pressure to afford a foam, 500mg.

This intermediate azetidine, (100mg, 0.23mmol) and triethylamine (34μl, 0.25mmol) were dissolved in dichloromethane (6ml) at 0°C and acetyl chloride (17μl, 0.24mmol) was

added. The solvent was removed under reduced pressure. The residue was basified with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined organic layers were dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an eluant of dichloromethane:methanol:0.88 ammonia (95:5:0.5) to afford the title compound as a foam, 62mg.

Found C, 68.31; H, 7.46; N, 13.75%

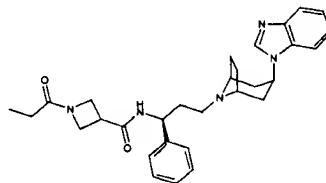
$\text{C}_{29}\text{H}_{35}\text{N}_5\text{O}_2 \cdot 1\text{H}_2\text{O} \cdot 0.1\text{CH}_2\text{Cl}_2$ requires C, 68.25; H, 7.32; N, 13.67%

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.60-1.68 (2H, m), 1.84 (3H, s), 1.94-2.10 (6H, m), 2.27-2.39 (2H, m), 2.55-2.74 (2H, m), 3.16-3.29 (1H, m), 3.32-3.42 (2H, m), 4.03-4.24 (3H, m), 4.35-4.45 (1H, m), 4.65-4.76 (1H, m), 5.16-5.27 (1H, m), 6.87-6.94 and 7.00-7.13 (1H, m), 7.23-7.32 (5H, m), 7.32-7.44 (3H, m), 7.76-7.82 (1H, m), 8.03-8.06 (1H, m)

LRMS: m/z 486.0 (MH^+)

EXAMPLE 37

N-{[(1*S*)-3-[3-*endo*-(1*H*-Benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-1-propionyl-3-azetidinecarboxamide



The title compound was prepared from the title compound of preparation 73 and propionyl chloride using a similar procedure to that described in example 36 in 55% yield.

Found C, 70.19; H, 7.62; N, 13.60%

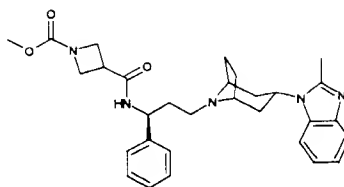
$\text{C}_{30}\text{H}_{37}\text{N}_5\text{O}_2 \cdot 0.8\text{H}_2\text{O}$ requires C, 70.09; H, 7.57; N, 13.62

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.06-1.13 (3H, t), 1.60-1.68 (2H, m), 1.92-2.13 (8H, m), 2.29-2.39 (2H, m), 2.53-2.74 (2H, m), 3.18-3.32 (1H, m), 3.32-3.42 (2H, m), 4.05-4.23 (3H, m), 4.35-4.45 (1H, m), 4.66-4.76 (1H, m), 5.16-5.27 (1H, m), 6.84-6.94 and 7.06-7.13 (1H, m), 7.23-7.32 (5H, m), 7.32-7.44 (3H, m), 7.76-7.82 (1H, m), 8.03-8.06 (1H, m)

LRMS: m/z 500.0 (MH^+)

EXAMPLE 38

Methyl 3-[[[(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]amino)carbonyl]-1-azetidinecarboxylate



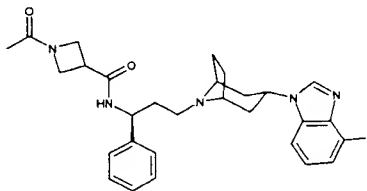
Methyl chloroformate (11 μ l, 0.14mmol) was added to a solution of the title compound of example 31 (64mg, 0.14mmol) and triethylamine (21 μ l, 0.15mmol) in dichloromethane (5ml). The reaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure and the residue taken up in ethyl acetate, washed with brine, dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane:methanol:0.88 ammonia (98:2:0.25 to 90:5:0.5) to afford the title compound as a white solid, 20mg.

^1H NMR (400 MHz, CDCl_3): δ [ppm] 1.69 (2H, bm), 1.78 (2H, bd), 1.95-2.18 (4H, m), 2.46-2.70 (8H, m), 3.16 (1H, m), 3.44 (2H, bs), 3.64 (3H, s), 4.06-4.14 (2H, m), 4.14-4.24 (2H, m), 4.57 (1H, m), 5.13 (1H, m), 7.12-7.23 (3H, m), 7.28-7.32 (3H, m), 7.33-7.42 (1H, m), 7.53 (1H, m), 7.68 (1H, m)

LRMS: m/z 516.3 (MH^+)

EXAMPLE 39

1-Acetyl-N-((1S)-3-[3-exo-(4-fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide



The title compound of preparation 89 (0.591g, 1.052mmol) and 4M hydrochloric acid in dioxane (10ml) were stirred for 1 hour. The excess of solvent was evaporated under reduced pressure to give a cream solid, which was added to glacial acetic acid (0.072ml, 1.263mmol), diisopropyl ethylamine (0.75ml, 4.21mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.242g, 1.263mmol), and 1-hydroxybenzotriazole hydrate (0.171g, 1.263mmol) in dichloromethane (8ml). The reaction mixture was stirred at room temperature for 16 hours, concentrated and dissolved in ethyl acetate then washed with 10% sodium carbonate solution. The organic layer was dried (MgSO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an eluent of dichloromethane: methanol (99:4) to afford the title compound as a white powder, 0.160g.

Found C, 65.28; H, 6.87; N, 13.410%

C₂₉H₃₄FN₅O₂ · 1.7H₂O requires C, 65.20; H, 7.06; N, 13.11

¹H NMR (400MHz, CDCl₃): δ [ppm] 1.75-2.70 (16H, m), 3.24 (1H, m), 3.56 (2H, m), 4.02-4.22 (3H, m), 4.40 (1H, m), 4.58 (1H, m), 5.12 (1H, q), 7.02 (1H, m), 7.10-7.42 (7H, m),

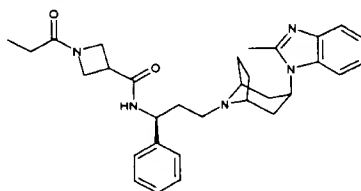
5 8.0 (1H, s)

LRMS: m/z 505 (MH⁺)

[α]_D -59.0° (c = 1.0, MeOH)

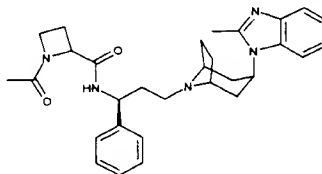
10 The following compounds have been prepared using methods similar to those described above:

N-{(1*S*)-3-[3-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide



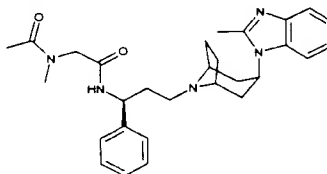
15

1-Acetyl-*N*-{(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-2-azetidinecarboxamide



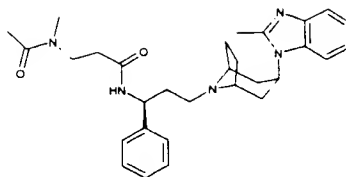
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2-[Acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide

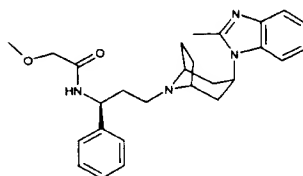


25

3-[Acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide

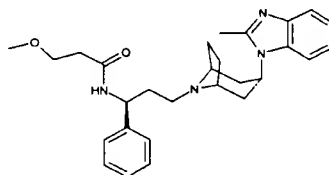


2-Methoxy-N-((1S)-3-[3-endo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)acetamide



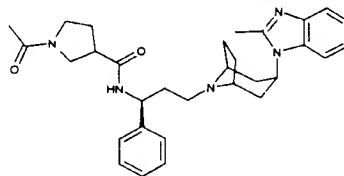
5

3-Methoxy-N-((1S)-3-[3-endo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)propanamide



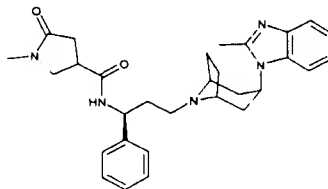
10

1-Acetyl-N-((1S)-3-[3-endo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-pyrrolidinecarboxamide



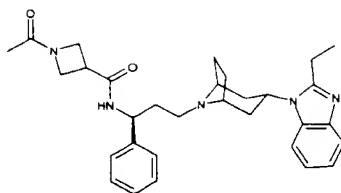
15

1-Methyl-N-((1S)-3-[3-endo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-2-oxo-4-pyrrolidinecarboxamide

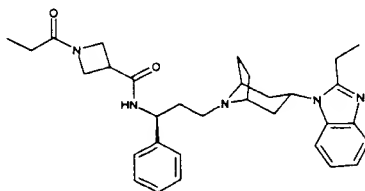


20

1-Acetyl-N-((1S)-3-[3-exo-(2-ethyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide

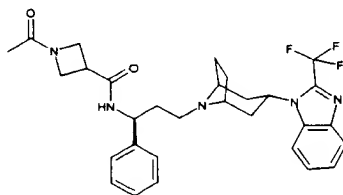


N-((1*S*)-3-[3-exo-(2-Ethyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-1-propionyl-3-azetidinecarboxamide



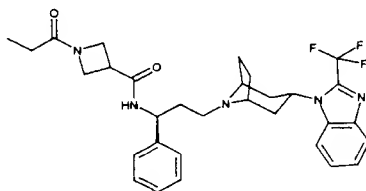
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1-Acetyl-*N*-((1*S*)-1-phenyl-3-{3-exo-[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]oct-8-yl}propyl)-3-azetidinecarboxamide



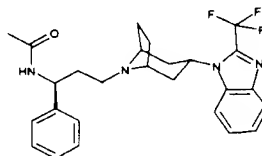
10

N-((1*S*)-1-Phenyl-3-{3-exo-[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]oct-8-yl}propyl)-1-propionyl-3-azetidinecarboxamide

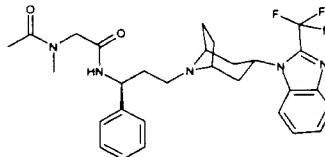


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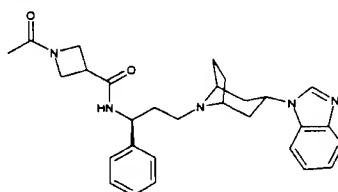
N-((1*S*)-1-Phenyl-3-{3-exo-[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]oct-8-yl}propyl)acetamide



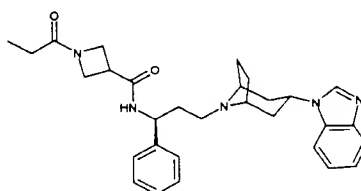
2-[Acetyl(methyl)amino]-N-((1S)-1-phenyl-3-{3-exo-[2-(trifluoromethyl)-1H-benzimidazol-1-yl]-8-azabicyclo[3.2.1]oct-8-yl}propyl)acetamide



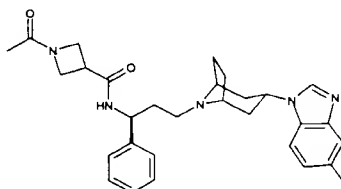
5 1-Acetyl-N-((1S)-3-[3-exo-(1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide



10 N-((1S)-3-[3-exo-(1H-Benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-1-propionyl-3-azetidinecarboxamide

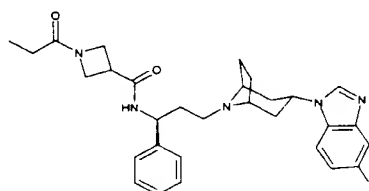


1-Acetyl-N-((1S)-3-[3-exo-(5-fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide

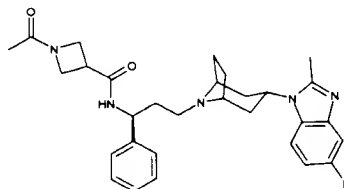


15

N-((1S)-3-[3-exo-(5-Fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-1-propionyl-3-azetidinecarboxamide

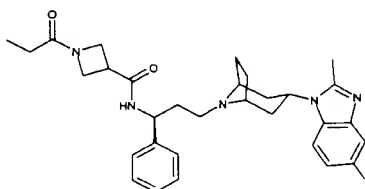


1-Acetyl-N-[(1S)-3-[3-exo-(5-fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-azetidinecarboxamide



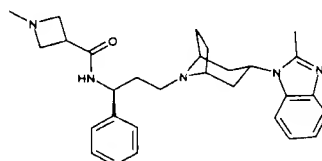
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N-[(1S)-3-[3-exo-(5-Fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-1-propionyl-3-azetidinecarboxamide



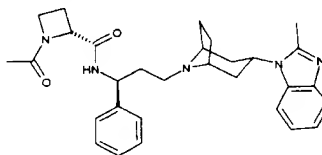
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1-Methyl-N-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-azetidinecarboxamide



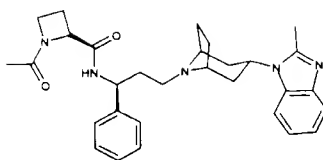
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(2S)-1-Acetyl-N-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-2-azetidinecarboxamide

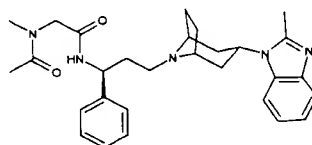


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(2R)-1-Acetyl-N-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-2-azetidinecarboxamide

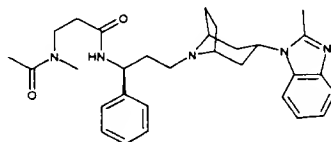


[Acetyl(methyl)amino]-N-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]acetamide



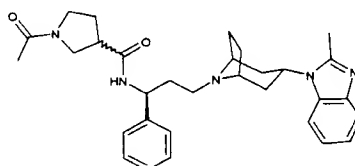
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[Acetyl(methyl)amino]-N-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]propanamide



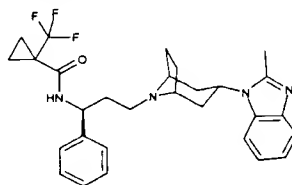
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1-Acetyl-N-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-pyrrolidinecarboxamide



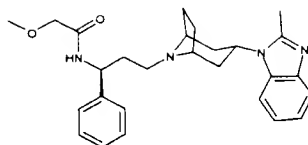
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[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-1-(trifluoromethyl)cyclopropanecarboxamide

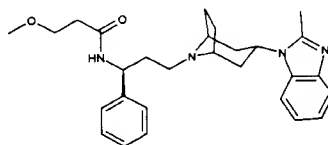


2-Methoxy-N-[(1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]acetamide

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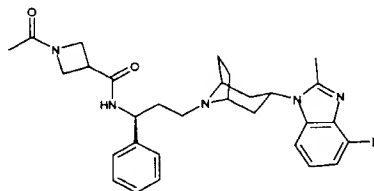


3-Methoxy-N-((1S)-3-[3-exo-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)propanamide



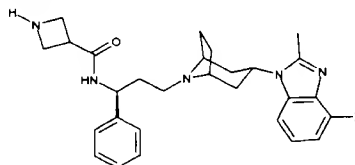
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1-Acetyl-N-((1S)-3-[3-exo-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide



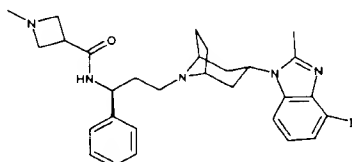
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N-((1S)-3-[3-exo-(4-Fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide



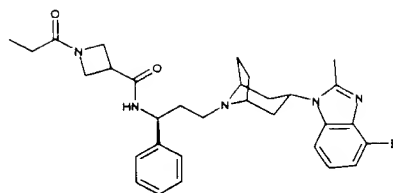
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1-Methyl-N-((1S)-3-[3-exo-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-azetidinecarboxamide

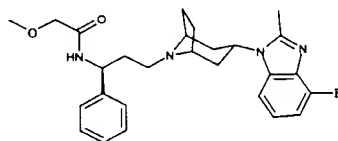


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N-((1S)-3-[3-exo-(4-Fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-1-propionyl-3-azetidinecarboxamide

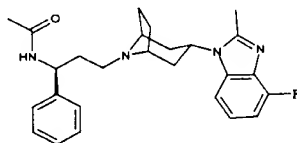


2-Methoxy-N-((1S)-3-[3-exo-(4-Fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)acetamide



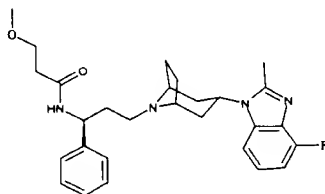
5

N-((1S)-3-[3-exo-(4-Fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)acetamide



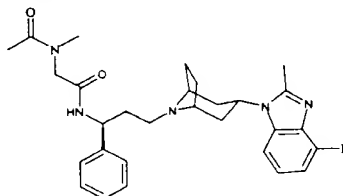
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3-Methoxy-N-((1S)-3-[3-exo-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)propanamide



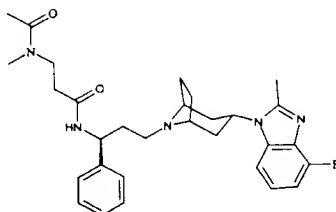
15

2-[Acetyl(methyl)amino]-N-((1S)-3-[3-exo-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)acetamide

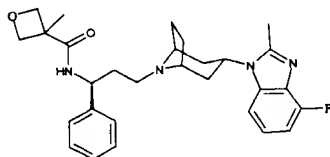


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3-[Acetyl(methyl)amino]-N-((1S)-3-[3-exo-(4-fluoro-2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)propanamide

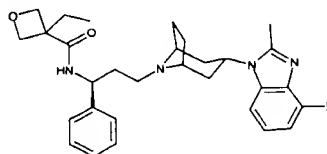


N-((1*S*)-3-[[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-methyl-3-oxetanecarboxamide



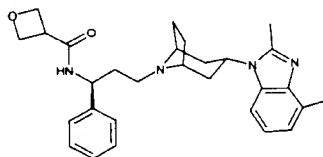
5

3-Ethyl-*N*-((1*S*)-3-[[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-oxetanecarboxamide



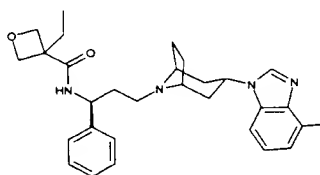
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N-((1*S*)-3-[[3-*exo*-(4-Fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-oxetanecarboxamide

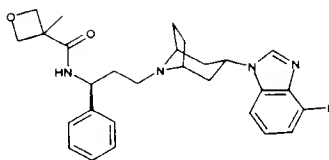


3-Ethyl-*N*-((1*S*)-3-[[3-*exo*-(4-fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-oxetanecarboxamide

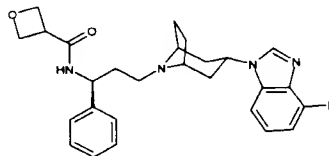
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N-((1*S*)-3-[[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-3-methyl-3-oxetanecarboxamide

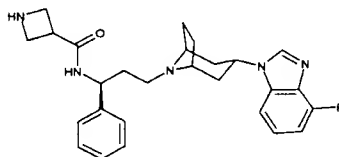


N-((1*S*)-3-((3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl)-3-oxetanecarboxamide



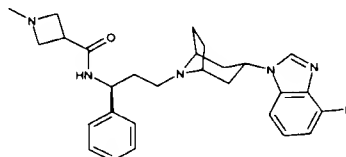
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N-((1*S*)-3-((3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl)-3-azetidinecarboxamide



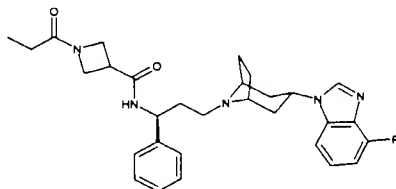
10

N-((1*S*)-3-((3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl)-1-methyl-3-azetidinecarboxamide



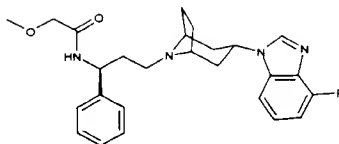
15

N-((1*S*)-3-((3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl)-1-propionyl-3-azetidinecarboxamide

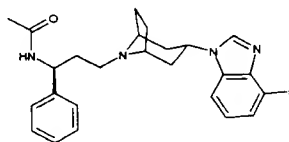


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N-((1*S*)-3-((3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl)-2-methoxyacetamide

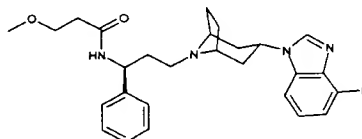


N-((1S)-3-[3-exo-(4-Fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)acetamide



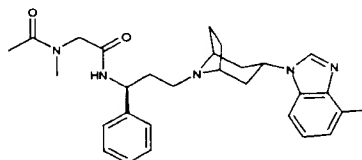
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N-((1S)-3-[3-exo-(4-fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)-3-methoxypropanamide



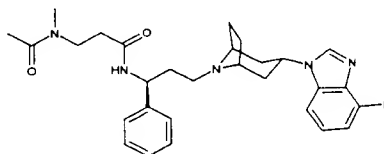
10

2-[Acetyl(methyl)amino]-N-((1S)-3-[3-exo-(4-fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)acetamide



15

3-[Acetyl(methyl)amino]-N-((1S)-3-[3-exo-(4-fluoro-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl)propanamide



20

CLAIMS

1. A compound of Formula (I);

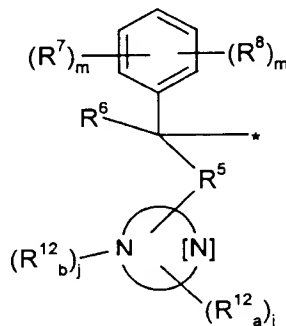
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wherein $[\text{R}_{\text{region } \alpha}]$ is selected from the group consisting of:

-A. Aryl heterocyclyl substituent components comprising:

10 --1. hetero-phenylmethylene moieties of partial Formula (1.0.0):



(1.0.0)

---wherein: the symbol " * " indicates the point of attachment of the moiety of partial Formula (1.0.0) to $\text{R}_{\text{region } \beta}$, as hereinafter defined;

15 --- R^5 is a member selected from the group consisting of a direct bond; $-\text{O}-$; $-\text{C}(=\text{O})-$; $-\text{NR}^4-$; and $-\text{S}(=\text{O})_p-$; where:

--- R^4 is hydrogen or $(\text{C}_1 . \text{C}_2)\text{alkyl}$;

--- R^6 is a member selected from the group consisting of hydrogen; $(\text{C}_1 . \text{C}_2)\text{alkyl}$; $(\text{C}_1 . \text{C}_2)\text{alkoxy}$; $-\text{CN}$; $-\text{OH}$; and $-\text{C}(=\text{O})\text{NH}_2$;

20 ---j is an integer selected from 0, 1, and 2;

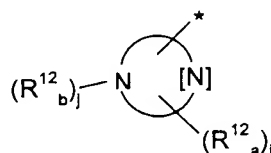
---m is an integer selected from 0, 1, and 2;

--- R^7 and R^8 are each a member selected from the group consisting of $-\text{F}$; $-\text{Cl}$; $-\text{CO}_2\text{R}^4$; $-\text{OH}$; $-\text{CN}$; $-\text{CONR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{OR}^4_b$; $-\text{NR}^4_a\text{S}(=\text{O})_p\text{R}^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_a\text{R}^4_b$; $(\text{C}_1 . \text{C}_4)\text{alkyl}$, and $(\text{C}_1 . \text{C}_4)\text{alkoxy}$ wherein said alkyl and alkoxy are each substituted with 0 to 3 substituents independently selected from F and Cl;
 25 $(\text{C}_1 . \text{C}_2)\text{alkoxycarbonyl}$; $(\text{C}_1 . \text{C}_2)\text{alkylcarbonyl}$; and $(\text{C}_1 . \text{C}_2)\text{alkylcarbonyloxy}$; where:

---p is an integer selected from 0, 1, and 2;

---R⁴_a and R⁴_b are each independently selected from hydrogen and (C₁.C₂)alkyl;

---the moiety represented by partial Formula (1.0.1):



5

(1.0.1)

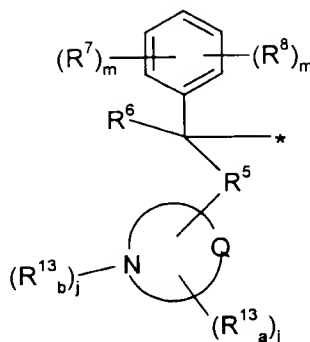
in partial Formula (1.0.0) represents a monocyclic heterocyclic group, or a bicyclic benzo-fused ring system containing said heterocyclic group wherein said heterocyclic group contains a total of 5- or 6- members of which one or two of said members is nitrogen, the presence of the optional second nitrogen atom being represented by: "[N]";
 10 wherein said heterocyclic group or ring system are selected from the group consisting of pyrrolyl; pyrazolyl; imidazolyl; pyridinyl; pyrazinyl; pyrimidinyl; pyridazinyl; piperazinyl; indolyl; indazolyl; benzimidazolyl; quinolyl; *iso*-quinolyl; and quinazolinyl; wherein:

---R¹²_a is a member selected from the group consisting of hydrogen; F; Cl; -CO₂R⁴; oxo; -OH; CN; NH₂; NH(C₁.C₂)alkyl; N(C₁.C₂)₂dialkyl; -CF₃; (C₁.C₄)alkyl; (C₂.C₄)alkenyl;
 15 (C₁.C₄)alkoxy; (C₃.C₇)cycloalkyl; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R⁹ where:

---R⁹ is a member independently selected from the group consisting of F; Cl; -CO₂R⁴; -OH; cyano; -CONR⁴_aR⁴_b; -NR⁴_aR⁴_b; -NR⁴_aC(=O)R⁴_b; -NR⁴_aC(=O)OR⁴_b; -NR⁴_aS(=O)_pR⁴_b; -S(=O)_pNR⁴_aR⁴_b; (C₁.C₄)alkyl including dimethyl, and (C₁.C₄)alkoxy wherein said alkyl
 20 and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; (C₁.C₂)alkoxycarbonyl; (C₁.C₂)alkylcarbonyl; and (C₁.C₂)alkylcarbonyloxy; and

---R¹²_b is absent or is a member selected from the group consisting of hydrogen; (C₁.C₄)alkyl; (C₂.C₄)alkenyl; (C₁.C₂)alkoxy; (C₃.C₇)cycloalkyl; and phenyl; wherein said
 25 alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R⁹ wherein R⁹ has the same meaning as above, except that it is selected independently selected therefrom; and

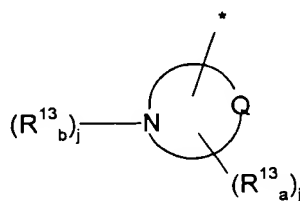
2. hetero-phenylmethylene moieties of partial Formula (1.1.0):



(1.1.0)

- wherein: the symbol “*”; R^5 ; R^6 ; R^7 ; R^8 ; j and m are as defined further above, except that
 5 all of the above-recited substituents are selected independently of their selection above;

—the moiety represented by partial Formula (1.1.1):



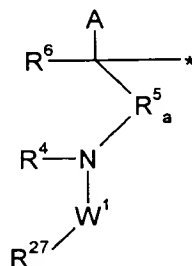
(1.1.1)

in partial Formula (1.1.0) represents:

- 10 —a. a monocyclic heterocyclic group containing a total of 5 or 6 members of which one said member is nitrogen and Q is selected from O and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; wherein said heterocyclic group is selected from the group consisting of oxazolyl; oxazolidinyl; isoxazolyl; thiazolyl; thiazolidinyl; *iso*-thiazolyl; morpholinyl; and thiomorpholinyl; or
- 15 —b. a monocyclic heterocyclic group containing a total of 5- or 6- member s of which two said members are nitrogen and a third or fourth said member is independently selected from N, O, and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; wherein said heterocyclic group is selected from the group consisting of triazolyl; triazinyl; tetrazolyl; oxadiazolyl; thiadiazolyl; and
- 20 — R^{13}_a is selected from the group consisting of hydrogen; F; Cl; $-CO_2R^4$; oxo; $-OH$; CN; NH_2 ; $NH(C_1-C_2)alkyl$; $N(C_1-C_2)_2dialkyl$; $-CF_3$; $(C_1-C_4)alkyl$; $(C_2-C_4)alkenyl$; $(C_1-C_2)alkoxy$; $(C_3-C_7)cycloalkyl$; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R^{11} where:
- 25 — R^{11} is a member selected from the group consisting of F; Cl; $-CO_2R^4$; $-OH$; $-CN$; $-CONR^4_aR^4_b$; $-NR^4_aR^4_b$; $-NR^4_aC(=O)R^4_b$; $-NR^4_aC(=O)OR^4_b$; $-NR^4_aS(=O)_pR^4_b$;

-S(=O)_pNR⁴_aR⁴_b; (C₁-C₄)alkyl including dimethyl, and (C₁-C₄)alkoxy wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; (C₁-C₂)alkoxycarbonyl; (C₁-C₂)alkylcarbonyl; and (C₁-C₂)alkylcarbonyloxy; and

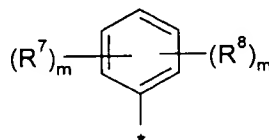
- 5 ----R¹³_b is a member selected from the group consisting of hydrogen; (C₁-C₄)alkyl; (C₂-C₄)alkenyl; (C₁-C₂)alkoxy; (C₃-C₇)cycloalkyl; C(=O)(C₁-C₄)alkyl; S(=O)₂(C₁-C₄)alkyl; and phenyl; wherein said alkyl, alkenyl, alkoxy, cycloalkyl and phenyl are substituted with 0 to 2 substituents R¹¹ wherein R¹¹ has the same meaning as in above, except that it is selected independently;
- 10 -B. a (substituted)-amido-aryl or -heterocyclyl moiety selected from the group consisting of
 --1. alkyl-, alkenyl-, and alkynyl-substituted-amido-aryl moieties of partial Formula (2.0.0):



(2.0.0)

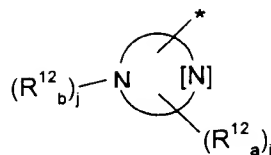
- wherein: the symbol " * "; R⁴ and R⁶; are as defined above, except that all of the above-recited substituents are selected independently of their selection above;
- 15

---A is a member selected from the group consisting of:
 ----1. the moiety of partial Formula (2.0.3)



(2.0.3)

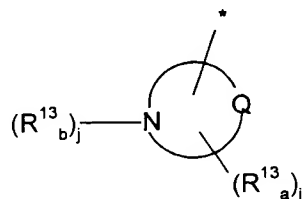
- 20 -----wherein: the symbol R⁷; R⁸ and m are as defined above, except that all of the above-recited substituents are selected independently of their selection above; and the symbol: " * " indicates the point of attachment of the moiety A to the, remaining portions of partial Formula (2.0.0);
- 2. the moiety of partial Formula (2.0.4)



(2.0.4)

which represents a monocyclic heterocyclic group, selected from the group consisting of pyrrolyl; pyrazolyl; imidazolyl; pyridinyl; pyrazinyl; pyrimidinyl; wherein: the symbol R^{12}_a and R^{12}_b are as defined above, except that all of the above-recited substituents are selected independently of their selection above; and the symbol: " * " indicates the point of attachment of the moiety A to the other, remaining portions of partial Formula (2.0.0);

---3. the moiety of partial Formula (2.0.5)



(2.0.5)

which represents

- a. a monocyclic heteroaromatic group containing a total of 5- members of which one said member is nitrogen and Q is selected from O and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; selected from the group consisting of oxazolyl; *isoxazolyl*; thiazolyl; and *iso*-thiazolyl; or
- b. a monocyclic heterocyclic group containing a total of 5- or 6- members of which two said members are nitrogen and a third or fourth said member is independently selected from N, O, and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; selected from the group consisting of triazolyl; triazinyl; tetrazolyl; oxadiazolyl; and thiadiazolyl; and
- wherein: the R^{13}_a , R^{13}_b and j are as defined above, except that all of the above-recited substituents are selected independently of their selection above; and the symbol: " * " indicates the point of attachment of the moiety A to the other, remaining portions of partial Formula (2.0.2);

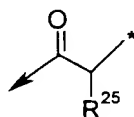
--- R^5_a is a member selected from the group consisting of a direct bond; $-C(=O)-$; and $-S(=O)_2-$;

--- W^1 is (1.) a direct bond; (2.) in the case where R^5_a is $-C(=O)-$ or $-S(=O)_2$, W^1 is a direct bond or $-(C_1-C_3)\text{alkylene-}$ wherein any single carbon atom thereof is substituted by 0 to 2 substituents R^{23} where R^{23} is a member selected from the group consisting of $-F$; $-Cl$;

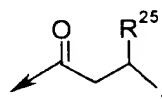
-CO₂R⁴; -OH; -CN; (C₁-C₄)alkoxy; (C₃-C₇)cycloalkyl; and phenyl; wherein said alkoxy, cycloalkyl, and phenyl are substituted with 0 to 2 substituents R¹¹, wherein said R¹¹ is as defined above, except that all of the above-recited substituents are selected independently of their selection above; or (3.) is a member independently selected from the group consisting of the moieties of partial Formulas (2.0.6) through (2.0.16), inclusive:



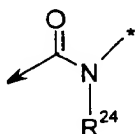
(2.0.6)



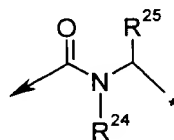
(2.0.7)



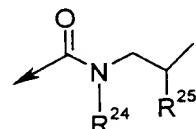
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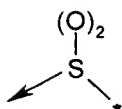
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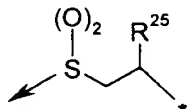
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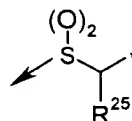
(2.0.11)



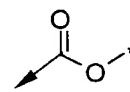
(2.0.12)



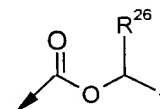
(2.0.13)



(2.0.14)



(2.0.15)



(2.0.16)

---wherein: the symbol: "→" indicates the point of attachment of the moiety W¹ to the nitrogen atom in partial Formula (2.0.0), and the symbol: "*" indicates the point of attachment of the moiety W¹ to the other, remaining portions of partial Formula (2.0.0); and R⁴ is as defined further above, but selected on an independent basis;

-----R²⁴ is selected from the group consisting of hydrogen and (C₁-C₄)alkyl; and

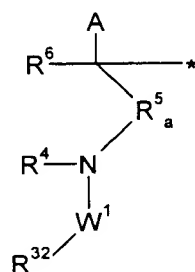
---R²⁵ and R²⁶ are each selected from the group consisting of -OH; (C₁-C₂)alkyl substituted by 0 to 3 substituents selected from F; and OH; and (C₁-C₂)alkoxy; and

---R²⁷ is selected from the group consisting of (C₁-C₆)alkyl; (C₂-C₆)alkenyl; and (C₂-C₆)alkynyl; wherein said alkyl, alkenyl, and alkynyl groups comprising R²⁷ are substituted with 0 to 3 substituents R²⁸ where:

---R²⁸ is selected from the group consisting of phenyl; F or Cl; oxo; hydroxy; (C₁-C₂)alkyl; (C₁-C₃)alkoxy; -C(=O)OR²⁹; -C(=O)(C₁-C₄)alkyl; -S(=O)₂(C₁-C₄)alkyl; -C(=O)NR²⁹R³⁰; -NR²⁹R³⁰; -NR²⁹C(=O)R³⁰; -NR²⁹C(=O)OR³⁰; -NR²⁹S(=O)_pR³⁰; and -S(=O)₂NR²⁹R³⁰, where:

---- R^{29} and R^{30} are each a member independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl substituted by 0 to 3 substituents selected from the group consisting of F and Cl;

--2. cycloalkyl-substituted-amido-aryl moieties of partial Formula (2.1.0):



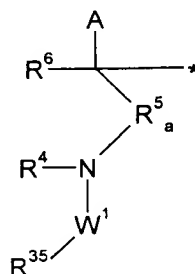
5

(2.1.0)

---wherein: A; W¹; the symbol " * "; R⁴; R⁵_a; and R⁶ have the same meaning as set out above, except that all of the above-recited substituents are selected independently of their selection above; and

- 10 ---R³² is a member selected from the group consisting of -(CH₂)_n-(C₃-C₇)cycloalkyl, where n is an integer selected from 0, 1, and 2; in the event n is 0, then the α-carbon atom of said (C₃-C₇)cycloalkyl is substituted by 0 or 1 (C₁-C₄)alkyl or phenyl, where said alkyl or phenyl are substituted by 0, 1, or 2 of CH₃, OCH₃, OH or NH₂; and in the event that n is 1 or 2, the resulting methylene or ethylene is substituted by 0 or 1 of F; NH₂; N(CH₃)₂; OH; OCH₃;
- 15 (C₁-C₄)alkyl; or phenyl; where said alkyl and phenyl are substituted by 0, 1, or 2 of CH₃, OCH₃, OH, and NH₂; and further wherein said (C₃-C₇)cycloalkyl is substituted by 0 to 3 substituents R²⁸ where R²⁸ is as defined further above, but selected independently

--3. aryl and heterocyclic-substituted-amido-aryl moieties of partial Formula (2.2.0):



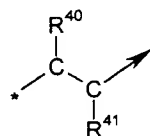
20

(2.2.0)

---wherein: A; W¹; the symbol: " * "; R⁴; R⁵_a; and R⁶ have the same meaning as set out above, except that all of the above-recited substituents are selected independently of their selection above; and

---R³⁵ is selected from the group consisting of phenyl; furyl; tetrahydrofuranyl; tetrahydropyranyl; oxetanyl; thienyl; pyrrolyl; pyrrolidinyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; imidazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; piperazinyl; pyrimidinyl; pyranyl; azetidiny; morpholinyl; parathiazinyl; indolyl; indolinyl; benzo[*b*]furanyl; 2,3-dihydrobenzofuranyl; benzothienyl; 1H-indazolyl; benzimidazolyl; benzoxazolyl; benzisoxazolyl; benzthiazolyl; quinolinyl; isoquinolinyl; phthalazinyl; quinazolinyl; and quinoxalinyl; wherein (1.) said group R³⁵ may be substituted upon any one or more carbon atoms thereof by 0 to 3 substituents R²⁸ where R²⁸ is as defined above, except that it is selected independently; (2.) said group R³⁵ is substituted with respect to any one or more nitrogen atoms thereof that is not a point of attachment of said aryl or heterocyclic moiety, by 0 to 3 substituents R¹³, where R¹³ is as defined above, except that it is selected independently; and (3.) said group R³⁵ with respect to any sulfur atom thereof that is not a point of attachment of said heterocyclic moiety, is substituted by 0 or 2 oxygen atoms;

15 [R_{region β}] is an alkyl bridging element of partial Formula (3.0.0):



(3.0.0)

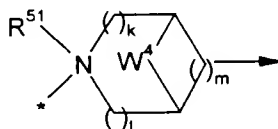
wherein:

--" * " is a symbol which represents the point of attachment of the moiety of partial Formula (3.0.0) to R_{region α};

--" → " is a symbol which represents the point of attachment of the moiety of partial Formula (3.0.0) to R_{region γ};

--R⁴⁰ and R⁴¹ are independently selected from the group consisting of hydrogen; (C₁-C₂) alkyl including dimethyl; hydroxy; and (C₁-C₃) alkoxy;

25 [R_{region γ}] is an aza-bicyclic moiety of partial Formula (4.2.0):



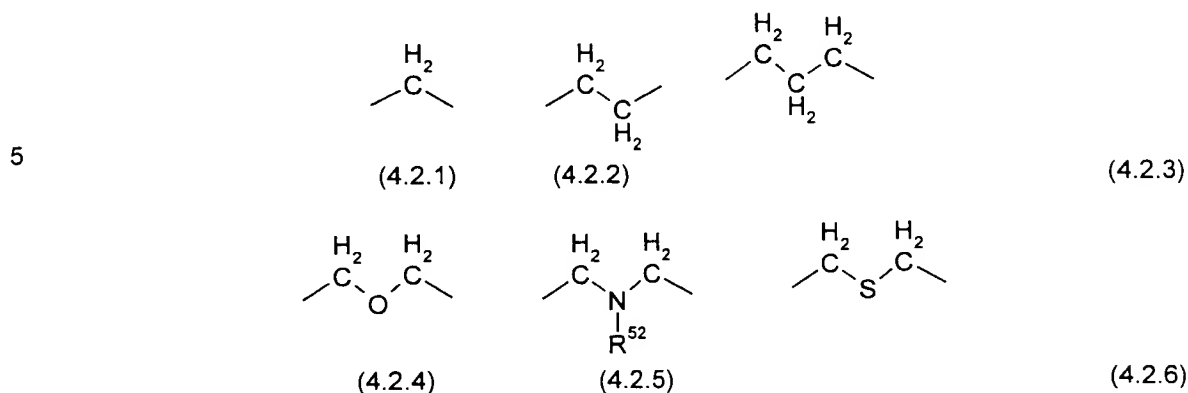
(4.2.0)

--wherein

--" * " is a symbol which represents the point of attachment of the moiety of partial Formula (4.2.0) to R_{region β};

--"→" is a symbol representing a covalent bond from any of the carbon atoms of the moiety of partial Formula (4.2.0) to $R_{\text{region } \delta}$;

-- W^4 is a direct bond; or is a member independently selected from the group consisting of partial Formulas (4.2.1) through (4.2.6):



--where:

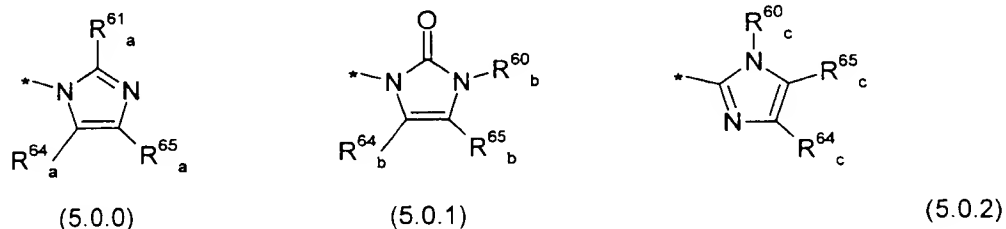
10 -- R^{52} is a member selected from the group consisting of hydrogen; phenyl; (C_1-C_4) alkyl substituted by 0 or 1 substituent independently selected from (C_1-C_2) alkoxy and $-CO_2R^4$; (C_3-C_6) cycloalkyl; $-CO_2R^4$; $\rightarrow O$; $C(=O)(C_1-C_3)$ alkyl; $-C(=O)NR^4_aR^4_b$; $-S(=O)(C_1-C_4)$ alkyl; and (C_1-C_2) alkylcarbonyl; where R^4 , R^4_a , and R^4_b are as defined above, but selected on an independent basis;

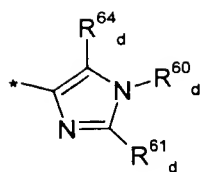
15 -- R^{51} is absent or is a member selected from the group consisting of (C_1-C_4) alkyl substituted by 0 or 1 substituent independently selected from (C_1-C_2) alkoxy and $-CO_2R^4$ where R^4 is as defined above; and $\rightarrow O$; it being understood that in the case where substituent R^{51} is present, the nitrogen atom is in quaternary form; and

-- k , l and m are each an integer selected from 0, 1, 2, and 3;

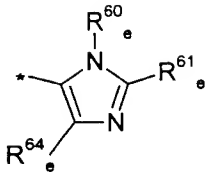
20 [$R_{\text{region } \delta}$] is a member selected from the group consisting of:

-A. a two-nitrogen-atom-containing five-membered heterocyclic moiety of partial Formulas (5.0.0) through (5.0.10):

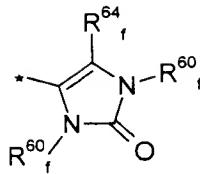




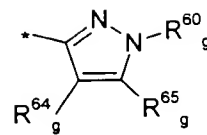
(5.0.3)



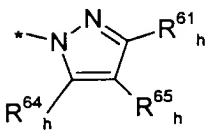
(5.0.4)



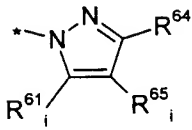
(5.0.5)



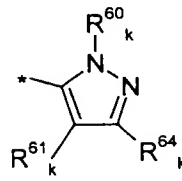
(5.0.6)



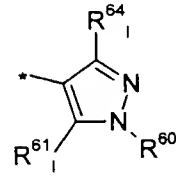
(5.0.7)



(5.0.8)



(5.0.9)



(5.0.10)

5

--wherein: the symbol: "*" indicates the point of attachment of each of the moieties of partial Formulas (5.0.0) through (5.0.10), inclusive, to $R_{\text{region Y}}$;

-- R^{60}_b through R^{60}_g , inclusive, R^{60}_k , and R^{60}_l are each a member selected from the group consisting of hydrogen; $-\text{CO}_2\text{R}^4$; $-\text{C}(=\text{O})\text{NR}^4_a\text{R}^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_a\text{R}^4_b$; where: R^4 , R^4_a , and R^4_b are as defined above but selected on an independent basis; $\rightarrow\text{O}$; $(\text{C}_1\text{--}\text{C}_2)\text{alkylcarbonyl}$; $-(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$; $-(\text{CH}_2)_n(\text{C}_3\text{--}\text{C}_7)\text{cycloalkyl}$; $-(\text{C}_2\text{--}\text{C}_3)\text{alkenyl}$; $-(\text{CH}_2)_n(\text{phenyl})$; and $-(\text{CH}_2)_n(\text{HET}_1)$, where n is an integer independently selected from 0, 1, and 2; wherein said $(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$, alkenyl, cycloalkyl, phenyl, and heterocyclyl groups are independently substituted with 0 to 3 substituents R^{66} , where:

15 -- HET_1 is a heterocyclyl group selected from the group consisting of thienyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; and morpholinyl; where:

20 --- R^{66} is a member selected from the group consisting of $-\text{F}$; $-\text{Cl}$; $-\text{OH}$; cyano; $-\text{C}(=\text{O})\text{OR}^{68}$; $-\text{C}(=\text{O})\text{NR}^{68}\text{R}^{69}$; $-\text{NR}^{68}\text{R}^{69}$; $-\text{NR}^{68}\text{C}(=\text{O})\text{R}^{69}$; $-\text{NR}^{68}\text{C}(=\text{O})\text{OR}^{69}$; $-\text{NR}^{68}\text{S}(=\text{O})_2\text{R}^{69}$; $-\text{S}(=\text{O})_2\text{NR}^{68}\text{R}^{69}$; $(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$ including dimethyl, and $(\text{C}_1\text{--}\text{C}_4)\text{alkoxy}$ wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl ; $(\text{C}_1\text{--}\text{C}_2)\text{alkoxycarbonyl}$; $(\text{C}_1\text{--}\text{C}_2)\text{alkylcarbonyl}$; and $(\text{C}_1\text{--}\text{C}_2)\text{alkylcarbonyloxy}$, where:

25 ---- R^{68} and R^{69} are each a member selected from the group consisting of hydrogen; and $(\text{C}_1\text{--}\text{C}_2)\text{alkyl}$; and where said:
 -- R^{61}_a ; R^{61}_d ; R^{61}_e ; and R^{61}_h through R^{61}_l inclusive; R^{64}_a through R^{64}_l inclusive; R^{65}_a through R^{65}_c inclusive; and R^{65}_g through R^{65}_i inclusive are each a member selected from the group consisting of hydrogen; $-\text{OH}$; $-\text{CF}_3$; cyano; $-(\text{C}_1\text{--}\text{C}_3)\text{alkoxy}$; $-\text{C}(=\text{O})\text{OR}^4$; $-\text{C}(=\text{O})\text{NR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{R}^4_b$; $-\text{NR}^4_a\text{C}(=\text{O})\text{OR}^4_b$; $-\text{NR}^4_a\text{S}(=\text{O})_p\text{R}^4_b$; $-\text{S}(=\text{O})_p\text{NR}^4_a\text{R}^4_b$; where: R^4 , R^4_a , and R^4_b are as defined further above but selected on an independent basis; $-(\text{C}_1\text{--}\text{C}_4)\text{alkyl}$;

$-(CH_2)_n-(C_3-C_7)$ cycloalkyl; $-(C_2-C_3)$ alkenyl; $-(CH_2)_n$ (phenyl); and $-(CH_2)_n$ (HET₁), where n is an integer selected from 0, 1, and 2; wherein said (C_1-C_4) alkyl, alkenyl, cycloalkyl, phenyl, and heterocyclyl groups where heterocyclyl groups is as defined above, are independently substituted with 0 to 3 substituents R^{66} where:

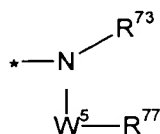
5 $--R^{66}$ is as defined above, or:

$--R^{64}_a$ through R^{64}_c inclusive; R^{64}_g through R^{64}_i inclusive; R^{65}_a through R^{65}_c inclusive; and R^{65}_g through R^{65}_i inclusive

may be taken together in their same subscript denominated pairs along with the remaining portions of the moieties of partial Formulas (5.0.0) through (5.0.2), and (5.0.6) through (5.0.8), to form a fused bicyclic ring system comprising a member
10 independently selected from the group consisting of benzimidazolyl; purinyl, *i.e.*, imidazopyrimidinyl; and imidazopyridinyl; wherein said fused bicyclic ring system is independently substituted with 0 to 3 substituents R^{66} , where R^{66} has the same meaning as set out further above, except that it is independently selected therefrom;

-B. a (substituted)-amide, carbamate, or urea moiety selected from the group consisting of:
15 of:

--1. alkyl-, cycloalkyl-, and alkenyl-(substituted)-amide, carbamate, or urea moieties of partial Formula (5.1.0):

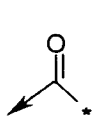


(5.1.0)

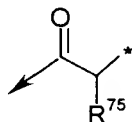
20 $--$ wherein: the symbol " $*$ " is as defined above;

$--R^{73}$ is a member selected from the group consisting of hydrogen and (C_1-C_2) alkyl;

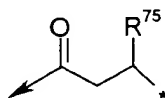
$--W^5$ is selected from the group consisting the moieties of partial Formulas (5.1.1) through (5.1.12):



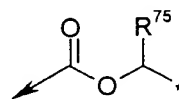
(5.1.1)



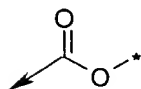
(5.1.2)



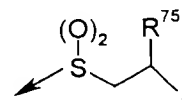
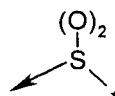
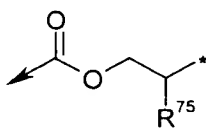
(5.1.3)

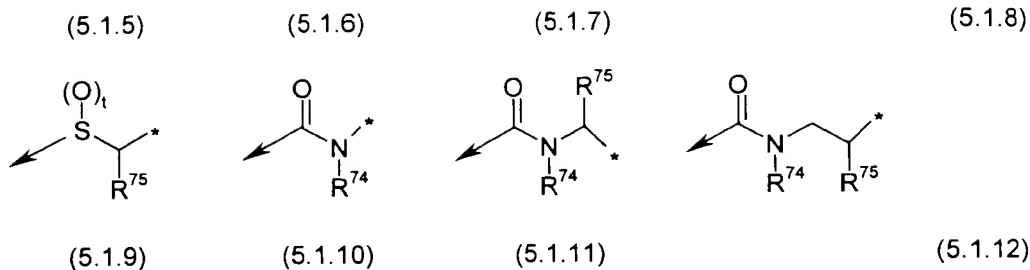


(5.1.4)



25





---wherein: the symbol: "→" indicates the point of attachment of the moiety W^5 represented by partial Formulas (5.1.1) through (5.1.12), inclusive, to the nitrogen atom in partial Formula (5.1.0), and the symbol: "*" indicates the point of attachment of the moiety W^5 to R^{77} as defined further below;

--- R^{74} and R^{75} are each selected from the group consisting of hydrogen; (C_1-C_2) alkyl substituted by 0 or 1 substituent independently selected from OH; and (C_1-C_2) alkoxy; and

10 --- R^{77} is a member selected from the group consisting of (C_1-C_6) alkyl; (C_2-C_6) alkenyl; and $-(CH_2)_n-(C_3-C_7)$ cycloalkyl, where n is an integer selected from 0, 1, and 2; and wherein said alkyl, alkenyl, and cycloalkyl groups comprising R^{77} are substituted with 0 to 3 substituents R^{78} , where:

--- R^{78} is a member selected from the group consisting of oxo; -OH; $-(C_1-C_2)$ alkyl; $-(C_1-C_3)$ alkoxy; $-CF_3$; $-C(=O)OR^{79}$; $-C(=O)NR^{79}R^{80}$; $-NR^{79}R^{80}$; $-NR^{79}C(=O)R^{80}$; $-NR^{79}C(=O)OR^{80}$; $-NR^{79}S(=O)_2R^{80}$; and $-S(=O)_2NR^{79}R^{80}$, where:

--- R^{79} and R^{80} are each a member independently selected from the group consisting of hydrogen; and (C_1-C_4) alkyl; and

20 --2. aryl and heterocyclyl-(substituted)-amide, carbamate, or urea moieties of partial Formula (5.2.0):



---wherein: the symbol: "*"; R^{73} ; and W^5 have the same meanings as under the definitions of partial Formula (5.1.0) above, except that they are independently selected therefrom; and

25 under W^5 the symbols: "→" and "*" are as defined under partial Formula (5.1.0); and

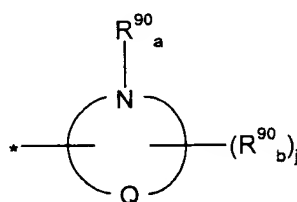
--- R^{82} is a member selected from the group consisting of phenyl; cinnolynyl; furyl; thienyl; pyrrolyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; imidazolyl; imidazolynyl; pyrazolyl; pyrazolynyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl;

parathiazinyl; indolyl; isoindolyl; indolinyl; benzo[b]furanyl; 2;3-dihydrobenzofuranyl; benzo[b]thiophenyl; 1H-indazolyl; benzimidazolyl; benzthiazolyl; quinoliny; isoquinoliny; phthalazinyl; quinazoliny; quinoxaliny; wherein:

5 ----the aryl or heterocyclyl moiety is substituted by 0 to 3 substituents R^{78} where R^{78} is as defined above, but selected on an independent basis; or

-C. a (substituted)-heterocyclyl moiety independently selected from the group consisting of:

--1. a heterocyclyl moiety of partial Formula (5.3.0):



10

(5.3.0)

--wherein: the symbol: "*" indicates the point of attachment of partial Formula (5.3.0) to $R_{\text{region } \gamma}$; Q is N, O or S and

--partial Formula (5.3.0) represents:

15 --a. a monocyclic heterocyclic group containing a total of 5- members of which one said member is nitrogen and a second said member is selected from O and S where said S may optionally be in the sulfonate form, wherein said heterocyclic group is selected from the group consisting of oxazolyl; isoxazolyl; thiazolyl; and iso-thiazolyl; or

20 ----b. a monocyclic heterocyclic group containing a total of 5- members of which two said members are nitrogen and a third or fourth said member is independently selected from N, O, and S where said S may optionally be in the sulfonate form, $-S(=O)_2$; wherein said heterocyclic group is independently selected from the group consisting of triazolyl; tetrazolyl; oxadiazolyl; and thiadiazolyl; and

25 -- R^{90}_a and R^{90}_b are each a member independently selected from the group consisting of hydrogen, $-(C_1.C_2)\text{alkylcarbonyl}$; $-(C_1.C_4)\text{alkyl}$; $-(CH_2)_n.(C_3.C_7)\text{cycloalkyl}$; $-(C_2.C_3)\text{alkenyl}$; $-(CH_2)_n.\text{(phenyl)}$; and $-(CH_2)_n.\text{(HET}_2\text{)}$, where n is an integer independently selected from 0, 1, and 2; wherein said $(C_1.C_4)\text{alkyl}$, alkenyl, cycloalkyl, phenyl, and HET_2 groups are independently substituted with 0 to 3 substituents R^{91} , where:

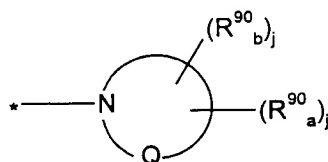
--j has the same meaning as set forth above, but is selected on an independent basis therefrom;

---HET₂ is a heterocyclyl group selected from the group consisting of thienyl; oxazolyl; isoxazolyl; thiazolyl; isothiazolyl; pyrazolyl; oxadiazolyl; thiadiazolyl; triazolyl; pyridyl; pyrazinyl; pyridazinyl; pyrimidinyl; parathiazinyl; and morpholinyl; where:

- 5 ---R⁹¹ is selected from the group consisting of -F; -Cl; -CO₂R⁴; -OH; -CN; -CONR⁹³R⁹⁴; -NR⁹³R⁹⁴; C(=O)(C₁-C₄)alkyl; -NR⁹³C(=O)R⁹⁴; -NR⁹³C(=O)OR⁹⁴; -NR⁹³S(=O)R⁹⁴; -S(=O)NR⁹³R⁹⁴; (C₁-C₄)alkyl including dimethyl, and (C₁-C₄)alkoxy wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from F and Cl; (C₁-C₂)alkoxycarbonyl; (C₁-C₂)alkylcarbonyl; and (C₁-C₂)alkylcarbonyloxy; wherein:

- 10 ----R⁹³ and R⁹⁴ are each a member independently selected from the group consisting of hydrogen; and (C₁-C₂)alkyl; and

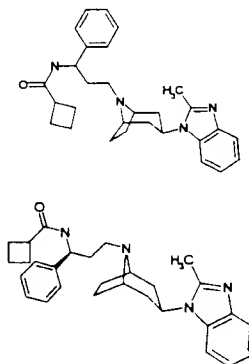
2. a heterocyclyl moiety of partial Formula (5.4.0):

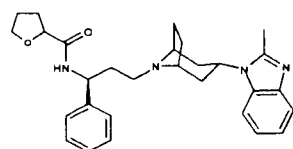
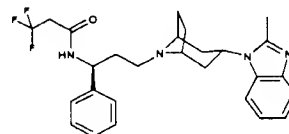
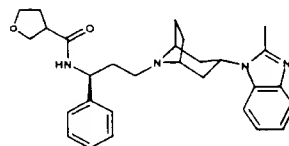
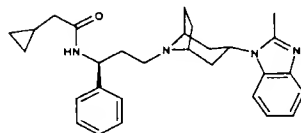
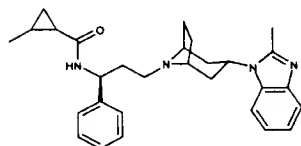
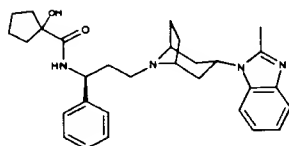
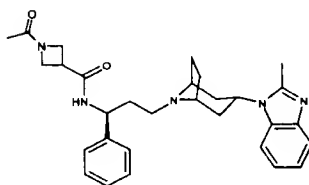
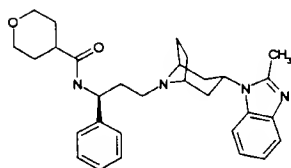
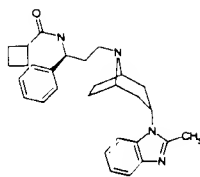


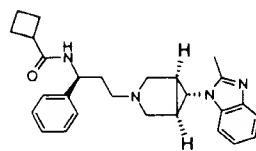
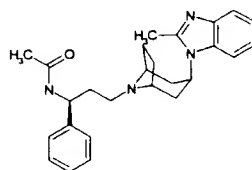
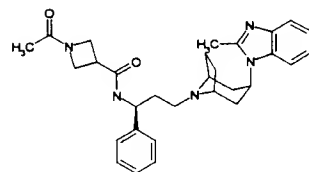
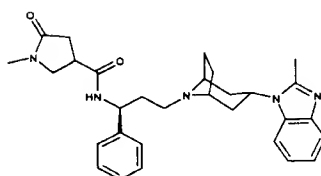
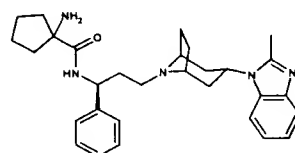
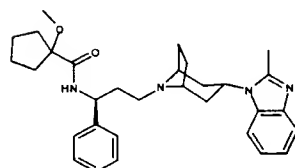
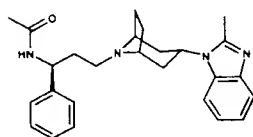
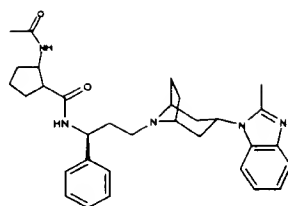
(5.4.0)

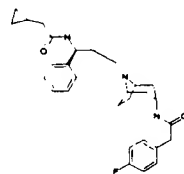
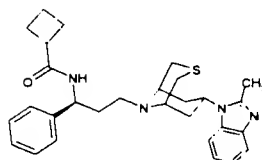
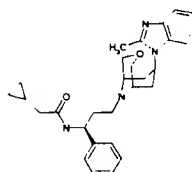
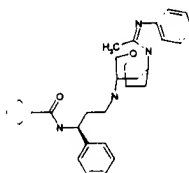
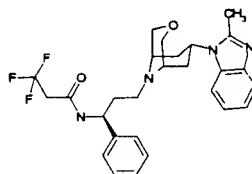
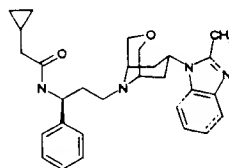
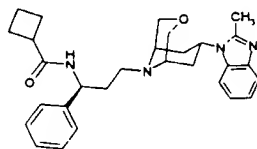
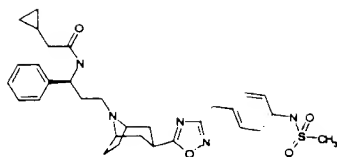
- 15 ---wherein: R^{90a}; R^{90b}; and j have the same meanings as set out above, but are selected independently.

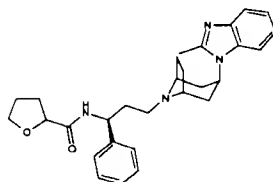
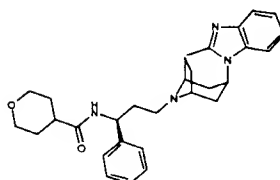
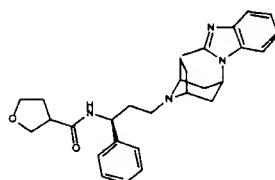
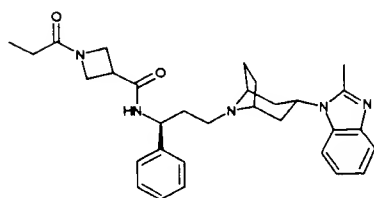
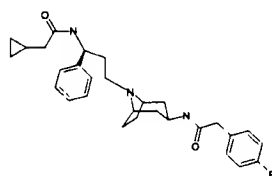
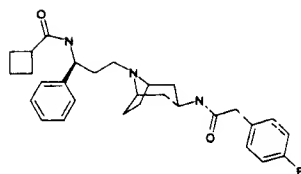
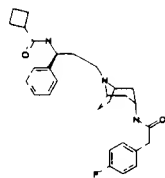
- 20 2. A compound which is selected from the group consisting of

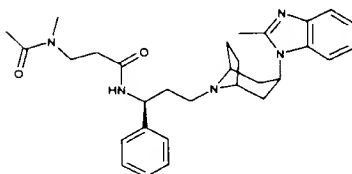
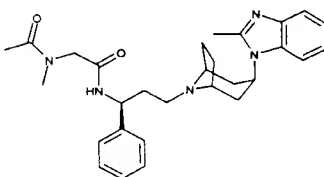
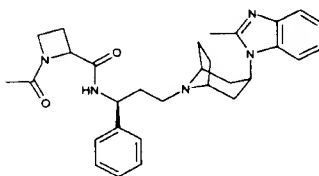
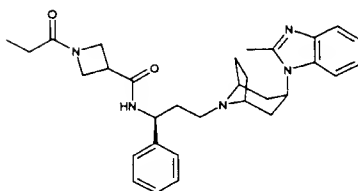
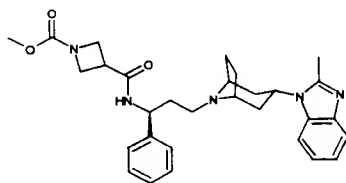
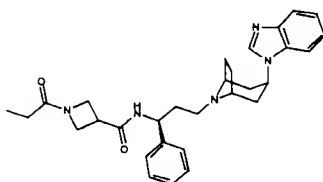
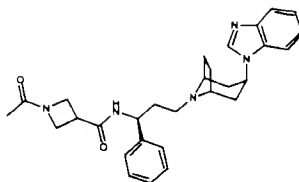


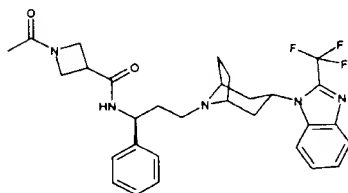
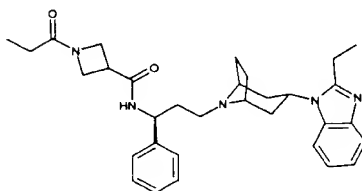
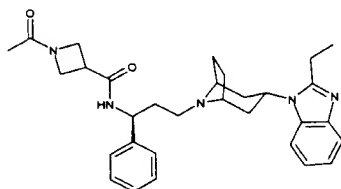
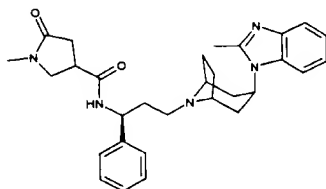
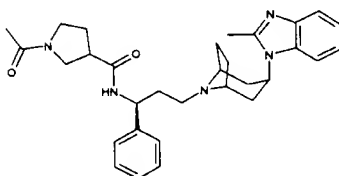
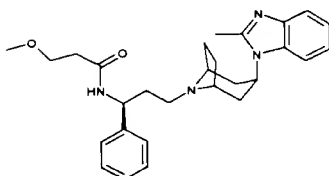
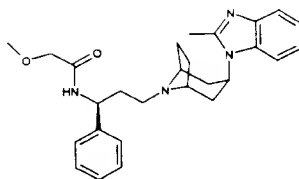


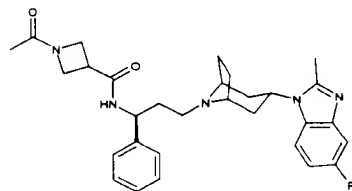
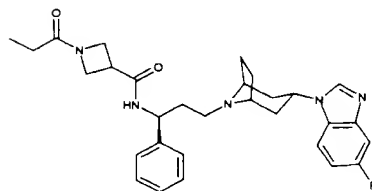
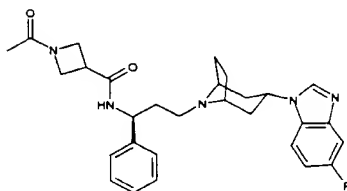
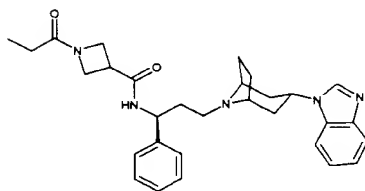
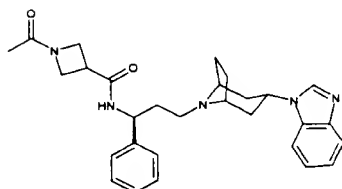
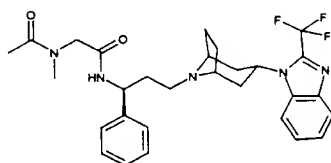
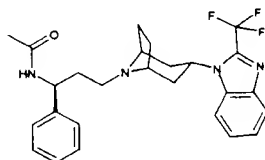
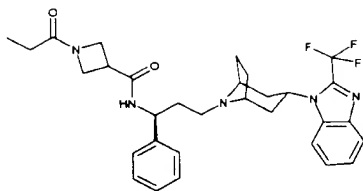


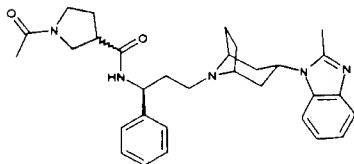
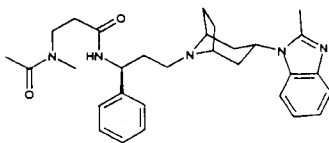
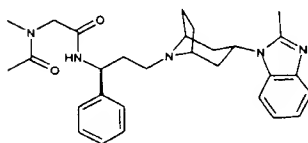
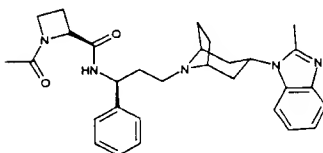
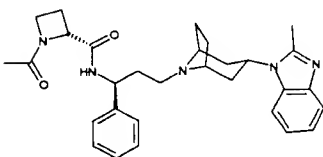
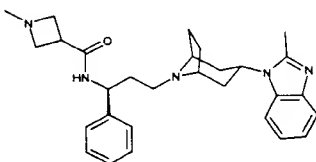
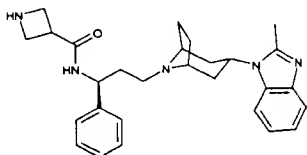
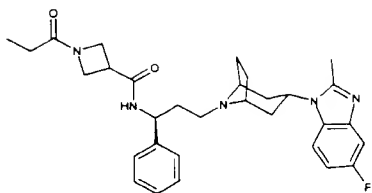


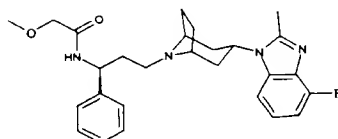
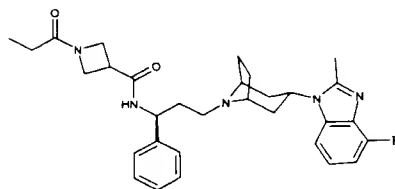
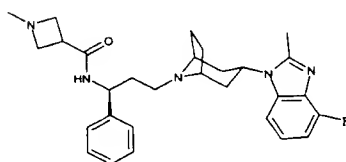
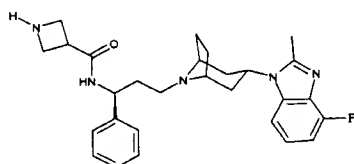
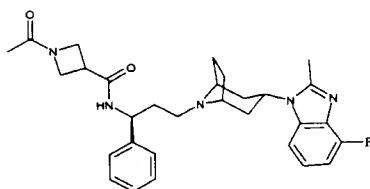
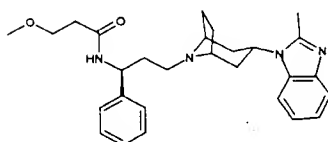
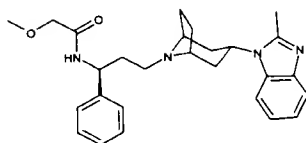
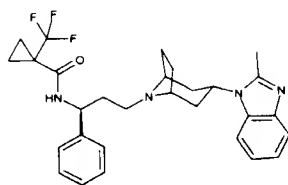


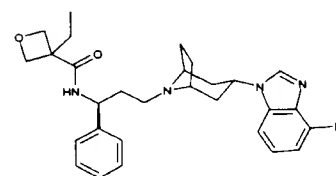
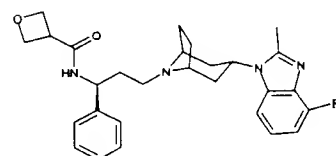
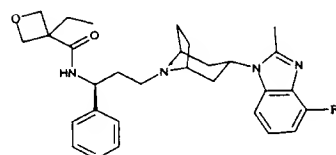
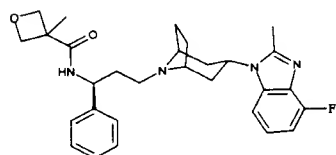
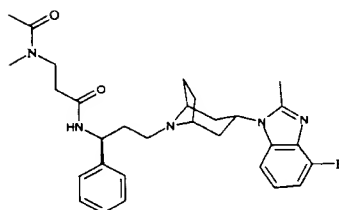
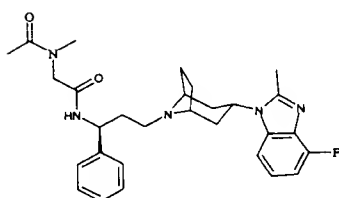
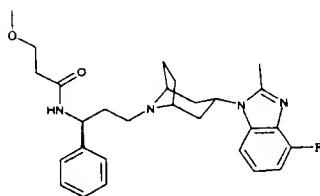
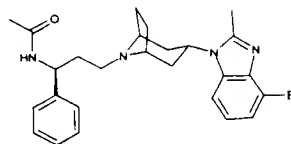


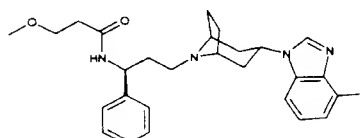
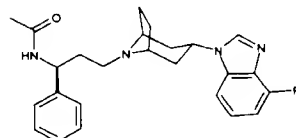
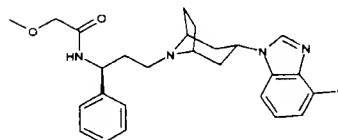
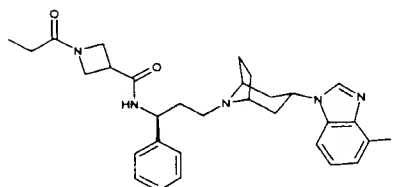
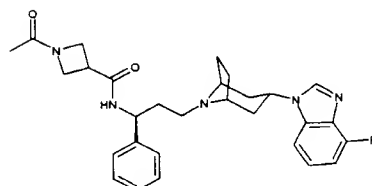
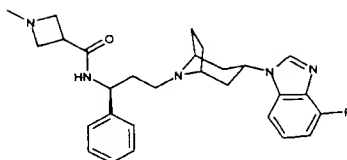
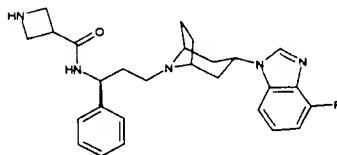
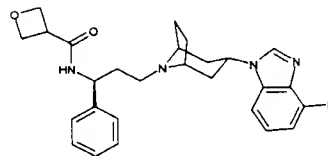
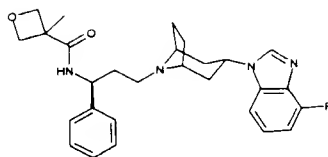


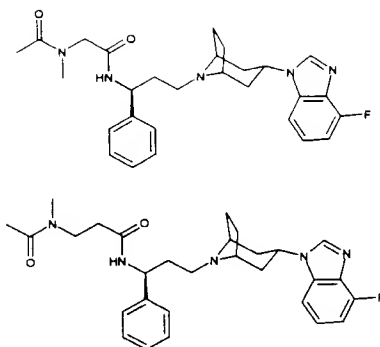












3. A compound which is selected from the group consisting of:

- 5 *N*-{3-[3-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide
- N*-{(1*S*)-3-[3-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide
- N*-{(1*S*)-3-[3-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide
- 10 *N*-{(1*S*)-3-[3-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}tetrahydro-2*H*-pyran-4-carboxamide
- 1-Acetyl-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenyl propyl}-3-azetidine carboxamide
- 1-Hydroxy-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenyl propyl}cyclopentanecarboxamide
- 15 2-Methyl-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenyl propyl}cyclopropanecarboxamide
- 2-Cyclopropyl-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 20 *N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}tetrahydro-3-furancarboxamide
- 3,3,3-Trifluoro-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide
- N*-{(1*S*)-3-[3-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}tetrahydro-2-furancarboxamide
- 25 1-(Acetylamino)-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide
- N*-{(1*S*)-3-[3-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide

- 1-Methoxy-*N*-{[(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide
- 1-Amino-*N*-{[(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide
- 5 1-Methyl-*N*-{[(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-2-oxo-4-pyrrolidinecarboxamide
- 1-Acetyl-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- N*-{[(1*S*)-3-[3-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 10 *N*-{[(1*S*)-3-[6-(2-Methyl-1*H*-benzimidazol-1-yl)-3-azabicyclo[3.1.0]hex-3-yl]-1-phenylpropyl}cyclobutanecarboxamide
- 2-Cyclopropyl-*N*-{[(1*S*)-3-[3-*exo*-(3-[4-[(methylsulfonyl)amino]benzyl]-1,2,4-oxadiazol-5-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 15 *N*-{[(1*S*)-3-[7-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl}cyclobutanecarboxamide
- 2-Cyclopropyl-*N*-{[(1*S*)-3-[7-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl}acetamide
- 3,3,3-Trifluoro-*N*-{[(1*S*)-3-[7-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl}propanamide
- 20 *N*-{[(1*S*)-3-[7-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl}cyclobutanecarboxamide
- 2-Cyclopropyl-*N*-{[(1*S*)-3-[7-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-3-oxa-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl}acetamide
- 25 *N*-{[(1*S*)-3-[7-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-3-thia-9-azabicyclo[3.3.1]non-9-yl]-1-phenylpropyl}cyclobutanecarboxamide
- 2-Cyclopropyl-*N*-{[(1*S*)-3-(3-*endo*-{[2-(4-fluorophenyl)acetyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl}acetamide
- N*-{[(1*S*)-3-(3-[3-*endo*-(4-Fluorophenyl)propanoyl]amino)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide
- 30 *N*-{[(1*S*)-3-(3-[3-*exo*-(4-Fluorophenyl)propanoyl]amino)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide
- 2-Cyclopropyl-*N*-{[(1*S*)-3-(3-*exo*-{[2-(4-fluorophenyl)acetyl]amino}-8-azabicyclo[3.2.1]oct-8-yl)-1-phenylpropyl}acetamide
- 35 *N*-{[(1*S*)-3-[3-*exo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide

- N*-{[(1*S*)-3-[3-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}tetrahydro-3-furancarboxamide
- N*-{[(1*S*)-3-[3-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}tetrahydro-2*H*-pyran-4-carboxamide
- 5 *N*-{[(1*S*)-3-[3-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}tetrahydro-2-furancarboxamide
- 1-Acetyl-*N*-{[(1*S*)-3-[3-*endo*-(1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- 10 *N*-{[(1*S*)-3-[3-*endo*-(1*H*-Benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide
- Methyl 3-[[[(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]amino]carbonyl]-1-azetidinecarboxylate
- N*-{[(1*S*)-3-[3-*endo*-(2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide
- 15 1-Acetyl-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-2-azetidinecarboxamide
- 2-[Acetyl(methyl)amino]-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 20 3-[Acetyl(methyl)amino]-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide
- 2-Methoxy-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 3-Methoxy-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide
- 25 1-Acetyl-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-pyrrolidinecarboxamide
- 1-Methyl-*N*-{[(1*S*)-3-[3-*endo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-2-oxo-4-pyrrolidinecarboxamide
- 30 1-Acetyl-*N*-{[(1*S*)-3-[3-*exo*-(2-ethyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- N*-{[(1*S*)-3-[3-*exo*-(2-Ethyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide
- 1-Acetyl-*N*-{[(1*S*)-1-phenyl-3-[3-*exo*-(2-(trifluoromethyl)-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]propyl}-3-azetidinecarboxamide
- 35 *N*-{[(1*S*)-1-Phenyl-3-[3-*exo*-(2-(trifluoromethyl)-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]propyl}-1-propionyl-3-azetidinecarboxamide

- N*-((1*S*)-1-Phenyl-3-{3-*exo*-[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]oct-8-yl}propyl)acetamide
- 2-[Acetyl(methyl)amino]-*N*-((1*S*)-1-phenyl-3-{3-*exo*-[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]-8-azabicyclo[3.2.1]oct-8-yl}propyl)acetamide
- 5 1-Acetyl-*N*-{(1*S*)-3-[3-*exo*-(1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- N*-{(1*S*)-3-[3-*exo*-(1*H*-Benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide
- 1-acetyl-*N*-{(1*S*)-3-[3-*exo*-(5-fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- 10 1-phenylpropyl}-3-azetidinecarboxamide
- N*-{(1*S*)-3-[3-*exo*-(5-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide
- 1-Acetyl-*N*-{(1*S*)-3-[3-*exo*-(5-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- 15 *N*-{(1*S*)-3-[3-*exo*-(5-Fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide
- N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- 1-methyl-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- 20 (2*S*)-1-acetyl-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-2-azetidinecarboxamide
- (2*R*)-1-acetyl-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-2-azetidinecarboxamide
- 25 2-[acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 3-[acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide
- 1-acetyl-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-pyrrolidinecarboxamide
- 30 1-phenylpropyl}-3-pyrrolidinecarboxamide
- N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-(trifluoromethyl)cyclopropanecarboxamide
- 2-methoxy-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 35 3-methoxy-*N*-{(1*S*)-3-[3-*exo*-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide

- 1-Acetyl-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
N-{(1*S*)-3-[3-*exo*-(4-Fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
- 5 1-Methyl-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
N-{(1*S*)-3-[3-*exo*-(4-Fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide
2-Methoxy-*N*-{(1*S*)-3-[3-*exo*-(4-Fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
- 10 *N*-{(1*S*)-3-[3-*exo*-(4-Fluoro-2-Methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
3-Methoxy-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide
- 15 2-[Acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide
3-[Acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide
N-{(1*S*)-3-[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-methyl-3-oxetanecarboxamide
- 20 3-Ethyl-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-oxetanecarboxamide
N-{(1*S*)-3-[3-*exo*-(4-Fluoro-2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-oxetanecarboxamide
- 25 3-Ethyl-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-oxetanecarboxamide
N-{(1*S*)-3-[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-methyl-3-oxetanecarboxamide
N-{(1*S*)-3-[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-oxetanecarboxamide
- 30 *N*-{(1*S*)-3-[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide
N-{(1*S*)-3-[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-methyl-3-azetidinecarboxamide
- 35 1-Acetyl-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-azetidinecarboxamide

N-{(1*S*)-3-[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-1-propionyl-3-azetidinecarboxamide

N-{(1*S*)-3-[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-2-methoxyacetamide

5 *N*-{(1*S*)-3-[3-*exo*-(4-Fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide

N-{(1*S*)-3-[3-*exo*-(4-fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-3-methoxypropanamide

10 2-[Acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}acetamide

3-[Acetyl(methyl)amino]-*N*-{(1*S*)-3-[3-*exo*-(4-fluoro-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}propanamide

4. A method of treating or preventing a disease or condition mediated by or
15 associated with modulation of CCR5 chemokine receptor activity in a patient which is in need of such treatment or is a prospective beneficiary of such prevention, comprising administering to said patient an amount of a compound claimed in any preceding claim which is therapeutically effective to treat or prevent said disease or condition.

20 5. A pharmaceutical composition for treating or preventing a disease or condition mediated by or associated with modulation of CCR5 chemokine receptor activity comprising an amount of a compound claimed in any preceding claim which is therapeutically effective to treat or prevent said disease or condition, together with a pharmaceutically acceptable carrier therefor.

25 6. A method of treating or preventing infection by human immunodeficiency virus (HIV) in a patient which is in need of such treatment or is a prospective beneficiary of such prevention, including treatment or prevention of acquired immunodeficiency syndrome (AIDS) resulting therefrom, comprising administering to said patient an amount of a compound as
30 claimed in any preceding claim which is therapeutically effective to treat or prevent said infection by HIV, including AIDS.

7. A method according to claim 5 further including coadministering to said patient in combination with a compound as claimed in any of claim 1 to 3, one or more
35 additional therapeutic agents for treating or preventing HIV infection comprising one or more members selected from the group consisting of (1) inhibitors of HIV protease; and (2) inhibitors of HIV reverse transcriptase.

8. A method according to claim 7 wherein: (1) said inhibitors of HIV protease comprise one or more members selected from the group consisting of indinavir, ritonavir, saquinavir, nelfinavir, and amprenavir; and (2) said inhibitors of HIV reverse transcriptase
5 comprise one or more members selected from the group consisting of (a) non-nucleoside reverse transcriptase inhibitors (NNRTIs) selected from nevirapine, delavirdine, and efavirenz; and (b) nucleoside/nucleotide inhibitors (NRTIs) selected from zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and adefovir dipivoxil.

10 9. A method according to claim 7 wherein said inhibitors of HIV protease and said inhibitors of HIV reverse transcriptase comprise one or more members selected from the group consisting of indinavir; ritonavir; saquinavir; nelfinavir; amprenavir; nevirapine; elavirdine; efavirenz; zidovudine; didanosine; zalcitabine; stavudine; lamivudine; abacavir; adefovir dipivoxil; FTC; PMPA; fozivudine tidoxil; talviraline; S-1153; MKC-442; MSC-204;
15 MSH-372; DMP450; PNU-140690; ABT-378; and KNI-764.

10. A method according to claim 7 wherein said method comprises preventing HIV infection and said patient being treated is aviremic and/or asymptomatic and is potentially or effectively infected with HIV, comprising administering to said patient a combination of
20 therapeutic agents comprising a member selected from the group consisting of: (i) a compound as claimed in claim 1; (ii) one non-nucleoside reverse transcriptase inhibitor (NNRTI) in addition to a compound of (I); (iii) one nucleoside/nucleotide inhibitor (NRTI) in addition to a compound of (I); (iv) one NRTI in addition to the combination of (ii); and (v) a compound selected from inhibitors of HIV protease used in place of said NRTI in
25 combinations (iii) and (iv).

11. A method according to claim 7 wherein said method comprises treating HIV infection and said patient being treated has detectable viremia or abnormally low CD4 counts, comprising administering to said patient a combination of therapeutic agents comprising (A) a
30 member selected from the group consisting of a compound of Formula (I) as defined in claim 1; and a therapeutic agent comprising one protease inhibitor in combination with two NRTIs; or (B) the combination of therapeutic agents recited in (A) where either said protease inhibitor component, or one or both of said NRTIs is/are replaced by a compound of Formula (I) as defined in claim 1.

35

12. A method according to claim 7 wherein said method comprises treating HIV-infected individuals that have failed antiviral therapy comprising administering to said patient a combination of therapeutic agents comprising (A) a member selected from the group

consisting of a compound as claimed in claim 1; or (B) a therapeutic agent comprising one protease inhibitor in combination with two NRTIs where either said protease inhibitor component, or one or both of said NRTIs is/are replaced by a compound of Formula (I) as defined in claim 1.

5

13. A method according to claim 8 further comprising coadministering with said compound of Formula (I) as defined in claim 1 one or more supplementary therapeutic agents which provide auxiliary treatment of diseases or conditions directly resulting from or indirectly accompanying infection by HIV, including AIDS resulting therefrom, wherein said
10 supplementary therapeutic agent is one or more members selected from the group consisting of proliferation inhibitors; immunomodulators; interferon or interferon derivatives; fusion inhibitors; integrase inhibitors; RNaseH inhibitors; and inhibitors of viral transcription and RNA replication.

15 14. A method according to claim 13 wherein said proliferation inhibitor is hydroxyurea; said immunomodulator is sargramostim; said fusion inhibitor is AMD3100, T-20, PRO-542, AD-349, or BB-10010; and said integrase inhibitor is AR177.

20 15. A pharmaceutical composition for treating or preventing infection by human immunodeficiency virus (HIV) in a patient which is in need of such treatment or is a prospective beneficiary of such prevention, including treatment or prevention of acquired immunodeficiency syndrome (AIDS) resulting therefrom, comprising an amount of a compound as claimed in claim 1 which is therapeutically effective to treat or prevent said infection by HIV or AIDS resulting therefrom, together with a pharmaceutically acceptable
25 carrier therefor.

16. A pharmaceutical composition according to claim 15 further including in combination with a compound of Formula (I) as claimed in claim 1, one or more additional therapeutic agents for treating or preventing HIV infection comprising one or more members
30 independently selected from the group consisting essentially of (1) inhibitors of HIV protease; and (2) inhibitors of HIV reverse transcriptase.

17. A pharmaceutical composition according to claim 16 wherein: (1) said inhibitors of HIV protease comprise one or more members independently selected from the
35 group consisting of indinavir, ritonavir, saquinavir, nelfinavir, and amprenavir; and (2) said inhibitors of HIV reverse transcriptase comprise one or more members selected from the group consisting of (a) non-nucleoside reverse transcriptase inhibitors selected from

nevirapine, delavirdine, and efavirenz; and (b) nucleoside/nucleotide inhibitors selected from zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and adefovir dipivoxil.

18. A pharmaceutical composition according to claim 16 wherein said inhibitors of
5 HIV protease and said inhibitors of HIV reverse transcriptase comprise one or more members selected from the group consisting of indinavir; ritonavir; saquinavir; nelfinavir; amprenavir; nevirapine; delavirdine; efavirenz; zidovudine; didanosine; zalcitabine, stavudine; lamivudine; abacavir; adefovir dipivoxil; FTC; PMPA; fozivudine todoxil; talviraline; S-1153; MKC-442; MSC-204; MSH-372; DMP450; PNU-140690; ABT-378; and KNI-764.

10

19. A pharmaceutical composition according to claim 15 further comprising
coadministering with said compound of Formula (1) as defined in claim 1 one or more
supplementary therapeutic agents which provide auxiliary treatment of diseases or conditions
directly resulting from or indirectly accompanying infection by HIV, including AIDS resulting
15 therefrom, wherein said supplementary therapeutic agent is one or more members selected from the group consisting of proliferation inhibitors; immunomodulators; interferon or interferon derivatives; fusion inhibitors; integrase inhibitors; RNaseH inhibitors; and inhibitors of viral transcription and RNA replication.

20

20. A pharmaceutical composition according to claim 19 wherein said proliferation inhibitor is hydroxyurea; said immunomodulator is sargramostim; said fusion inhibitor is AMD3100, T-20, PRO-542, AD-349 or BG-10010; and said integrase inhibitor is AR177.

21. A method of evaluating a putative HIV retrovirus mutant for resistance to anti-
25 HIV therapeutic agents, comprising isolating said putative mutant virus from an *in vitro* culture thereof; an *in vitro* animal infection model thereof; or from patient samples where said patient is undergoing optimal or sub-optimal treatment comprising administration of a compound as defined in claim 1, alone or together in any combination thereof with one or more therapeutic agents for treating or preventing HIV infection.

30

22. A mutant HIV virus or component part thereof, prepared in accordance with the procedures of claim 21.

23. A mutant HIV virus or component thereof according to claim 21 wherein said
35 component is the complete envelope protein thereof, or infections fragment thereof.

24. A method of discovering the presence of, and/or confirming the activity of a chemokine modulator having activity against a mutant HIV virus, comprising using as a probe

for effecting said discovery and/or confirmation a mutant HIV virus or component thereof according to claim 21.

25. A diagnostic agent for use in choosing a therapeutic regimen and/or
5 predicting the outcome for a patient being treated for infection by a mutant HIV virus, wherein
said diagnostic agent comprises a mutant HIV virus or component thereof according to claim
21.

26. A pharmaceutical composition for treating or preventing a respiratory disease or
condition comprising an amount of a compound claimed in any of claims 1 to 3 which is
10 effective to treat said disease or condition, together with a pharmaceutically effective carrier
therefor.

27. A compound as claimed in claims 1 to 3 in purified form.

28. A pharmaceutical composition comprising a compound as claimed in claims 1
15 to 3 and one or more inert excipients.

ABSTRACT

Compounds of Formula 1

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which are useful as modulators of chemokine activity. The invention also provides pharmaceutical formulations and methods of treatment using these compounds.